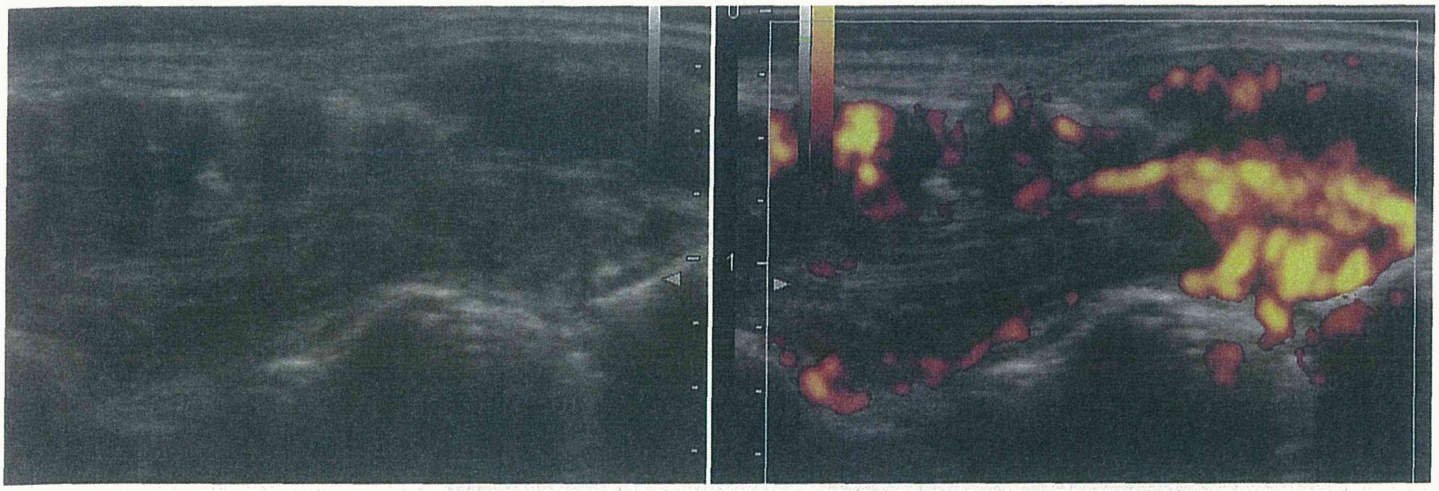
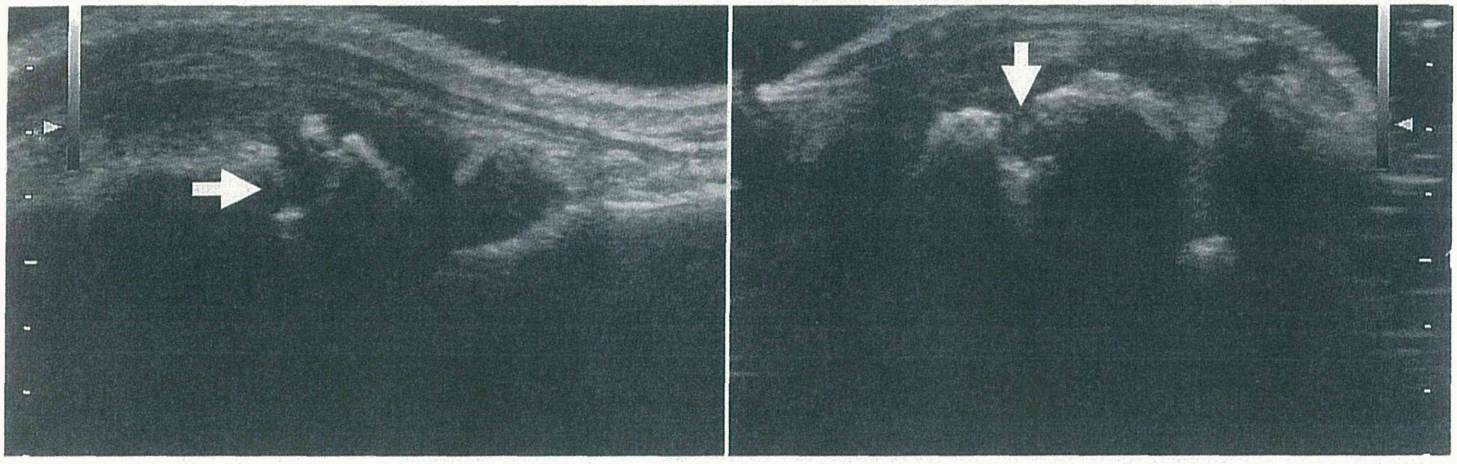


a．Bモード法で腱周囲の腱鞘が肥厚し，一部に滑液貯留も認められる．

b．PD法にて肥厚した腱鞘滑膜に一致して血流シグナルが検出できる．

図 6．尺側手根伸筋腱腱鞘滑膜炎



a．Bモード縦断像

b．Bモード横断像

図 7．第2中手骨頭の骨びらん(矢印)

して正しく腱を描出する必要がある．

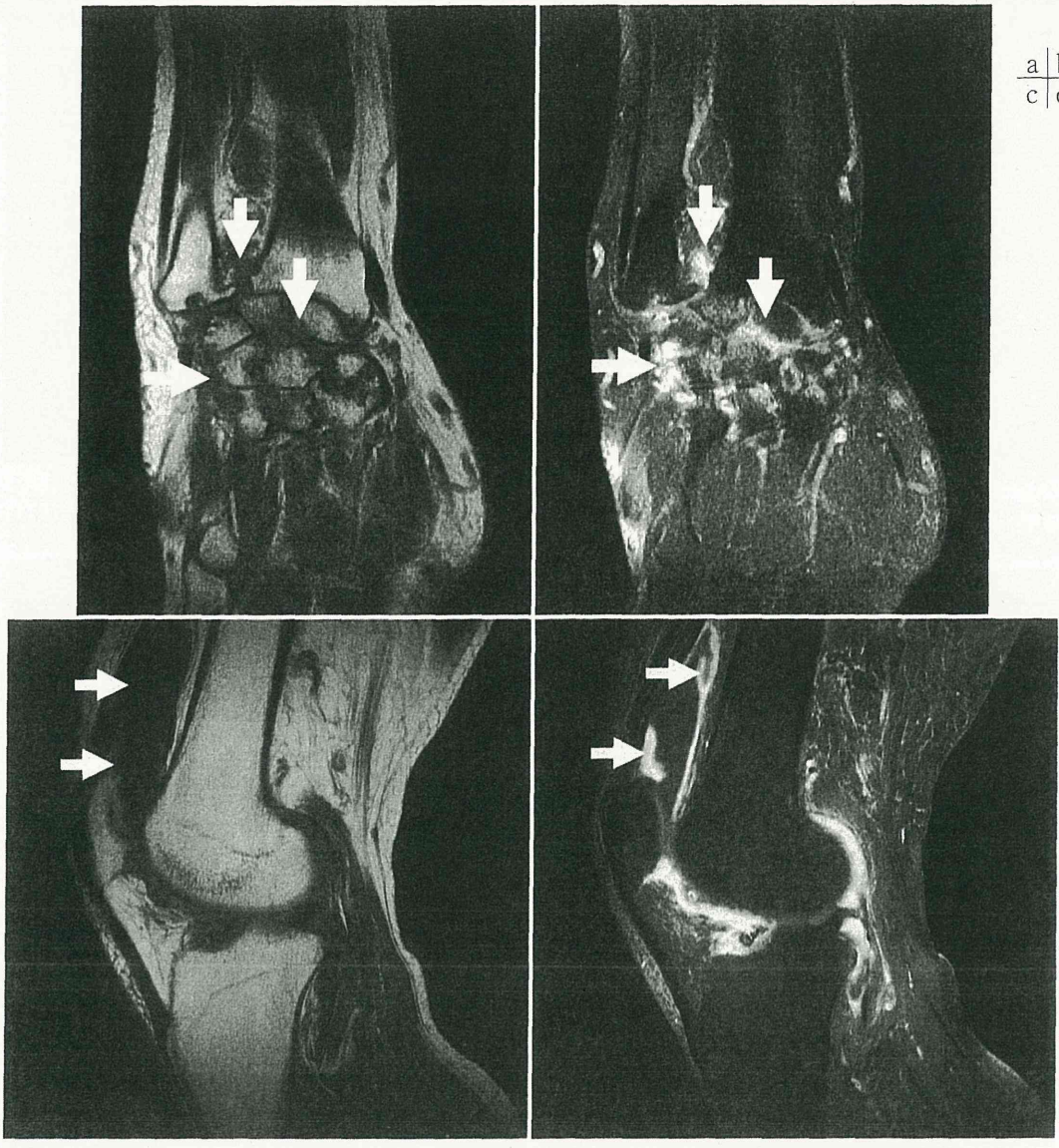
4）骨びらん

関節内の骨表の不連続点として観察されるが，縦断と横断の2平面での確認が必要である(図7)．超音波検査は撮像面を任意に選択できるため，早期の骨びらんの検出に有効と報告されている[5]．

3．早期診断と治療効果判定における超音波検査の意義

2010年ACR/EULARの新分類基準[6]を用いてRAを診断する場合，関節腫脹の確認が極めて重要である．超音波検査では不顕性の滑膜炎を効率よく描出できるため[7]，超音波検査を導入することでRAの超早期診断が可能となることが期待される．しかしながら，OA，SLE，乾癬性関節炎，痛風などRAと鑑別診断すべき疾患においてもPDシグナル陽性の滑膜炎を認めることがあるため，超音波検査を用いたRAの超早期診断にはより厳密な鑑別診断が要求される．

また，臨床的寛解に到達したと判断された症例においても，超音波検査にてPDシグナルが確認されることがある[8]．残存したPDシグナルはその後の関節破壊の進行[4]や疾患活動性の再燃[9]に関与することが報告されているため，超音波検査を用いた厳しい基準で寛解を評価・維持する必要性がある．



a｜b
c｜d

図 8.
MRI にて検出された滑膜炎
a，b：手関節，c，d：膝関節
a ：T1 強調像で低信号領域(矢印)を認める．
b ：脂肪抑制併用造影 T1 強調像にて造影された滑膜(矢印)が描出される．
c ：T1 強調像で低信号領域(矢印)を認める．
d ：脂肪抑制併用造影 T1 強調像にて造影された滑膜(矢印)と造影効果のない関節液を明瞭に区別することができる．

MRI
(magnetic resonance imaging)

1．基本的な撮像方法

T1 強調像，造影脂肪抑制 T1 強調像，脂肪抑制 T2 強調像もしくは STIR 像での 2 方向撮影(冠状断および横断像)が基本となる．

1）脂肪抑制画像

脂肪は T1，T2 強調像のいずれも高信号として描出される．脂肪抑制画像とは，この信号を抑制して低信号として描出する方法であり，選択的脂肪抑制法と STIR(short time inversion recovery)の 2 つに大別される．選択的脂肪抑制法は主に造影効果を明瞭に表したいときに用いられるが，低磁場の装置では脂肪抑制は得られにくい．一方，STIR は低磁場の装置でも均一な脂肪抑制が得られやすいが，造影剤によるエンハンス効果も抑制されるため造影 MRI では用いられない．

2）造影 MRI

造影剤(ガドリニウム)静注後，造影効果のある部位は T1 強調像で高信号として描出され，脂肪抑制を併用することで明瞭に確認することができる．造影効果は，組織の血流および血管の浸透性を反映する．

2．MRI で読み取るべき所見

1）滑膜炎

肥厚した滑膜は T1 強調像で低信号，T2 強調像で低～高信号で描出される．早期の滑膜炎は線維化が乏しく T2 強調像において高信号となるため，関節液と区別がつかない．造影 MRI 画像では造影された滑膜と造影効果のない関節液を明瞭に区別することができる．この際，選択的脂肪抑制

法を併用することが望ましい(図8). STIR像においても滑膜炎は高信号として検出されるが, 関節軟骨も高信号を呈するため, 結果として非造影MRIにおける滑膜炎検出の特異性を低下させる原因となっている[10].

2) 腱鞘炎

腱鞘滑膜の肥厚あるいは腱鞘内の滑液貯留として描出される. 肥厚した腱鞘滑膜の描出には造影MRIが有用である.

3) 骨侵食

骨皮質欠損およびその近傍の骨髄における限局性の異常信号(T1強調像で低信号, T2強調像で等～高信号, STIR像で高信号)として描出され, 造影MRIで造影効果が認められる(図9). MRI画像では単純X線写真に比して高率に骨侵食像が検出できるが[11], 健常者にも骨侵食様の所見が靱帯付着部や栄養孔の部分に認められることがある[12]. 造影効果がなく滑膜炎や骨髄浮腫を伴っていない場合は, 病的所見とは鑑別して評価する.

4) 骨髄浮腫

単純X線検査や超音波検査で検出することができず, MRIで初めて検出される病態である. MRIではT1強調像で低信号, T2強調像で等～高信号, STIR像で高信号を示す境界不明瞭な異常信号として認められ, 造影効果を示す(図10). 骨髄浮腫は単純X線写真で検出される骨びらんの前駆病変で, 関節破壊や関節機能を予測する重要な因子であることが報告されている[13].

a | b

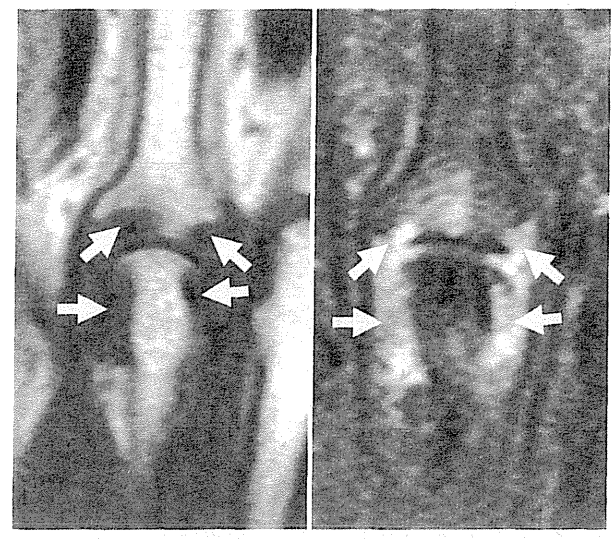
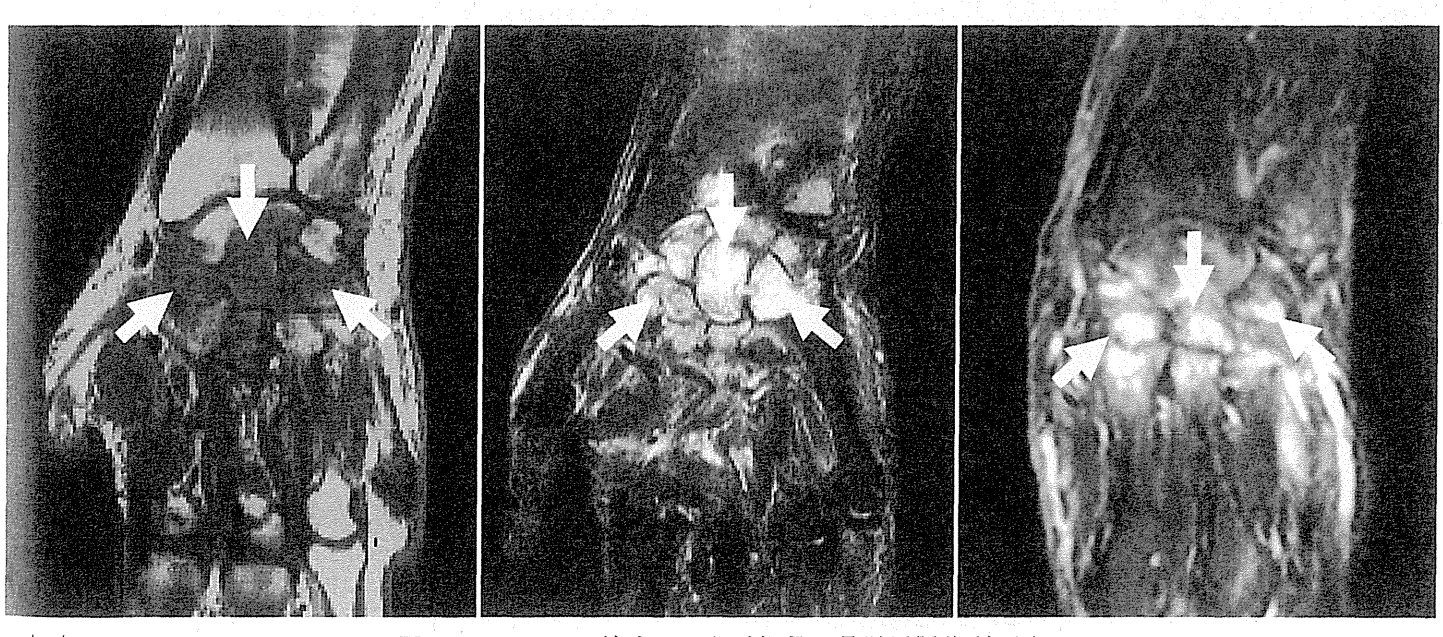


図9. MRIにて検出されたMCP関節の骨侵食像(矢印)
T1強調像で低信号(a)として描出され, 造影MRIで造影効果(b)が認められる.

3. RA早期診断への応用

診断未確定関節炎がRAに移行することを予測する際, MRI画像所見は有用である. 玉井ら[14]によると, 自己抗体(抗CCP抗体あるいはIgM-RF), MRI画像における対称性手・指滑膜炎, MRI画像における骨髄浮腫・骨侵食の3項目のう



a | b | c

図10. MRIにて検出された手根骨の骨髄浮腫像(矢印)
T1強調像で低信号(a), STIR像で高信号(b)を示す境界不明瞭な異常信号で, 造影効果(c)が認められる.

ち2項目以上陽性の場合，RAと診断できる感度は83%，特異度は85%，陽性予測値は93%，陰性予測値は67%，診断確度は83%であると報告されている．MRI画像を有効に活用すればRAの診断時期は間違いなく早まるであろう．

まとめ

RA診療における画像診断，特に単純X線検査，関節超音波検査およびMRIに焦点を当て，有用性と観察すべきポイントについて述べた．それぞれの画像検査の特性を踏まえ臨床に活用することが望まれるが，一方でRA診療が画像検査偏重に陥ることは避けたい．画像診断ツールは今後さらに改良され，より詳細な情報を我々は得ることができるようになると思われるが，RA診療には総合的，多面的なアプローチが要求される．臨床所見・血液検査所見に有効な画像検査が加わることでより質の高いRA診療が実践され，患者の生活の質が今後益々向上することが切望される．

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Ⅳ．治療
1．治療戦略
1）関節リウマチの診療ガイドライン

山中　寿

要　旨

診療ガイドラインとは，「特定の臨床状況において，適切な判断を行なうため，臨床家と患者を支援する目的で系統的に作成された文書」である．関節リウマチ診療においてもACRやEULARでガイドライン/リコメンデーションが作成され順次改訂されている．日本でも厚生労働省研究班によるガイドライン作成が進行中であり，日本リウマチ学会でもMTX使用法などに関するガイドラインを発表している．

〔日内会誌　101：2860～2864，2012〕

Key words　EBM，系統的文献検索

1．治療ガイドラインとは

診療ガイドラインとは，「特定の臨床状況において，適切な判断を行なうため，臨床家と患者を支援する目的で(assist practitioner and patient decisions) 系統的に作成された文書」(米国医学研究所 Institute of Medicine，1990) と定義されている．

ガイドライン（指針）に類する表現として，指令(directive)，規制(regulations)，推奨(recommendation) などがあるが，一般的には規制(regulations)＞指令（directive)＞推奨（recommendation)＞or＝指針（guideline）の順でより遵守が求められると考えられる．歴史的に見ると，診療ガイドラインはその名称から「拘束力を持つ」ものと暗黙のうちに了解されてきた[1]．しかしながら，上記の表現で明らかなように，ガイドラインはあくまで臨床的判断を支援するものであり，拘束するものでもなければ規制するものでもない．また多彩な症例が混在する臨床の現場においては不確実性のなかで診療が行われており，すべての診療がガイドライン通りに行われることはありえない．ガイドライン通りに行った結果が不幸な転機を取る可能性もありガイドラインに強制力を持たせることは不可能である．したがってガイドラインの内容が医師の裁量権を冒すものでもないし，ガイドライン通りの治療を選択しないことを理由として医師が責任を問われることもない．

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Rheumatoid Arthritis : Progress in Diagnosis and Treatment. Topics : IV. Treatment ; 1. Treatment Strategies, 1) Guidelines for the management of rheumatoid arthritis.

Hisashi Yamanaka : Institute of Rheumatology, Tokyo Women's Medical University, Japan.

関節リウマチ（rheumatoid arthritis：RA）の領域においては，ガイドライン（指針）とリコメンデーション（推奨）が混在しており，この両者はどう違うのかが多くの人々が持つ疑問である．北米ではガイドライン（指針）とリコメンデーション（推奨）は同等とされているが，ACRが2002年に発表したものはガイドラインでそれ以降はリコメンデーションである．一般にガイドラインは60～95％の患者に適応できる基準とされている[2]が，リコメンデーションはガイドラインに到達するための手段という意味合いが含まれるため，より拘束力は低いものの，より幅広い患者を対象とした文書と考えられる．

なお，リコメンデーションの和訳は「推奨」であって，「勧告」ではない．勧告は推奨より明らかに強制力を伴う用語であり，リコメンデーションを「勧告」と訳す場合は，そこに訳者の意図が含まれると考えて良い．つまり，リコメンデーションを「勧告」と訳す場合は，その内容が訳者にとって有利な内容を含んでいて，それを強制することが訳者にとって利益をもたらすものと考えるべきである．このようなものにも利益相反の問題が生じる可能性があることは認識するべきである．

現在では，非常に多くの診療ガイドラインが作成されている．しかしながら，ガイドライン作成方法自体も進化しており，現時点ではAGREE（Appraisal of Guidelines Research & Evaluation）に準拠して作成することが求められており，エビデンスの質の評価のみならず，作成されたガイドラインの質も評価される時代になっている．しかしながら，一概にガイドラインと言ってもその作成方法や客観性は玉石混交である．RA診療ガイドラインについても本稿で紹介するように多くのものがあるが，その作成方法はさまざまである．本稿では便宜的にガイドライン/リコメンデーションがどのような方法で作成されたかをレベル表記して紹介したい．

➢レベル1：薬剤の添付文書に記載された用法用量を基本にして，公表されたエビデンスを追加することにより，日常診療を支援する目的で作成されたもの．作成はAGREE準拠ではなく，系統的文献検索は行っていない．

➢レベル2：EBM（Evidence Based Medicine）に基づくガイドラインで，作成はAGREEに準拠して系統的文献検索を行い，そのうえで推奨度が決定されたもの．多くの診療ガイドラインはこのレベルである．

➢レベル3：新しいGRADE（Grading of Recommendations, Assessment, Development and Evaluation）法により作成されたもの．系統的文献検索によりエビデンスの質を評価したうえで，利益と不利益のバランス，患者の価値観や好み，医療費や医療資源の利用まで考慮して推奨度を決定するもの．今後の望まれるガイドライン作成法である．

2. ACR，EULARガイドライン/リコメンデーション

RA診療に関するACR（American College of Rheumatology：米国リウマチ学会）ガイドラインとしては，1996年に発表された2編が最初である．作成方法などについては明示されていないが，いずれもレベル1の手法を用いて作成されたと考えられ，網羅的な教科書的記載である[3,4]．

2002年のACRガイドラインは，1996年のガイドラインを薬物治療の進歩を勘案して改訂したものである．可能な限りエビデンスに基づくがいくつかの推奨はコンセンサスに基づき作成されたと記載されており，やはりレベル1の手法に留まっている[5]．

RA診療ガイドラインを大幅に進化させたのは，EULAR（European League against rheumatism：欧州リウマチ学会）を中心とするEBMを用いたガイドライン/リコメンデーション作成

の一連の業績である．EULARは学会内に作業部会（task force）を組織し，系統的文献検索（systematic literature review（SLR））と専門医の意見に基づいて，複数のリコメンデーションを作成した．作業部会は5つに分かれ，（a）低分子DMARDsの単剤投与かステロイドを含まない併用療法，（b）ステロイド剤単独か低分子DMARD（s）との併用，（c）生物学的DMARDs，（d）治療戦略（e）医療経済学的問題の5つの課題を担当し，複数のリコメンデーションを作成した[6~11]．

一方，ACRは同様にEBMに基づくリコメンデーションを発表した．これも同様に作業部会を立ち上げ，系統的文献検索を行ったうえで専門医の意見も取り入れたレベル2の方法論で作成されたものである[12]．

最も新しいリコメンデーションは，このACR 2008リコメンデーションの改訂版で，2012年5月に発表された[13]．Core Expert Panel（CEP）と患者代表も含むTask Force Panel（TFP）を立ち上げ，系統的論文検索を行ったうえでパネル会議，臨床シナリオを作成してDelphi法による合意形成などを行い，リコメンデーションを作成した．リコメンデーションは（1）DMARDや生物学的製剤の開始，中止，追加，変更など，（2）生物学的製剤を肝炎，悪性新生物，心不全などを有する患者に投与する場合，（3）生物学的製剤使用時の結核スクリーニング，（4）DMARDや生物学的製剤投与中のワクチン接種，についての推奨を記載している．特に，（2）（4）に関してはエビデンスレベルC（専門家の意見を主にしたコンセンサス）であるが，臨床的に問題となる点に対して学会として踏み込んだ推奨を提示しており，その姿勢は高く評価できる．

3. 日本のRA診療ガイドライン

日本におけるRA診療ガイドラインとしては，1997年に日本リウマチ財団が発行したものが最初である．これはリウマチ科の自由標榜が認められたことを契機としてレベル1の方法で作成されたものである．2004年にはこの改訂版が日本リウマチ財団から出版された[14]．これは1999年から開始された厚生労働省エビデンスに基づく診療ガイドライン作成研究班（班長：越智隆弘）により作成したものである．当初はレベル2の手法で作成が開始されたがRA領域のエビデンスが十分でなく，あくまで初版を改訂することを基本として作成された．ただし，薬物療法の分野に関しては系統的文献検索を行ったうえで推奨度を決定したので，かなりレベル2に近い方法論で作成された．現時点でも，RA診療全体をカバーするガイドラインとしては，これが最も新しいものである．このガイドライン導入前後におけるリウマチ医の診療パターンの変化も研究されている[15]．

その後，2011年度より厚生労働省研究班（我が国における関節リウマチ治療の標準化に関する多層的研究，研究代表者・宮坂信之）の分科会として関節リウマチ診療ガイドライン作成分科会が立ち上げられ，治療が大幅に変遷した現状を反映したRA診療ガイドラインを作成中である．山中寿が分科会長を務め，京都大学・中山健夫教授の指導を受けてGRADE法を用い，最も進歩したレベル3の手法を用いたガイドライン作成が進行中である．早ければ2013年春には予備案の作成を目指している．

4. JCR（日本リウマチ学会）診療ガイドライン

上記の総合的なガイドラインとは別にJCR（日本リウマチ学会）が作成した診療ガイドラインがいくつも発表されている．これらは新しく診療に導入された薬剤や臨床的に問題のある点に関して，JCR調査・研究委員会が臨床医の診療を支援する目的で作成したものである．いずれも

レベル１の方法を用いて作成されたもので，薬剤の用法用量を逸脱しない範囲における投与方法や投与上の注意点が記載されたものである．いずれも日本リウマチ学会ホームページに掲載されており，自由にダウンロードできるようになっているので，その活用範囲は広い．各々のガイドラインとURLを記載する．

1）MTX治療ガイドライン

http://www.ryumachi-jp.com/info/guideline_mtx.html

MTX治療ガイドラインは，公知申請により2011年２月にMTXの用法用量が変更されたのを機に日本リウマチ学会MTX診療ガイドライン策定小委員会が作成し，出版したものである[16]．

2）関節リウマチ（RA）に対するTNF阻害療法施行ガイドライン（2010年改訂版）

http://www.ryumachi-jp.com/info/guideline_TNF_100930.html

日本リウマチ学会・調査研究委員会の中の生物学的製剤使用ガイドライン策定小委員会では，TNF阻害薬がRAの治療に導入されて以来，新しい製剤のエビデンスが確立されるたびにガイドラインを改訂している．上記はその最新版であるが，TNF阻害薬全般に対する注意点の他，現時点で使用可能なインフリキシマブ，エタネルセプト，アダリムマブの３剤についての記載があるが，2011年に承認されたゴリムマブについても追加されることになると思われる．

3）関節リウマチ（RA）に対するトシリズマブ使用ガイドライン（2010年改訂版）

http://www.ryumachi-jp.com/info/guideline_TCZ_100716.html

トシリズマブは，抗IL-6受容体抗体で上記のTNF阻害薬とは異なった特性を有するうえに，日本発の薬剤であり，日本から情報を発信する必要性もあることから，日本リウマチ学会・調査研究委員会の中の生物学的製剤使用ガイドライン策定小委員会が別途ガイドラインを作成した．

4）関節リウマチ（RA）に対するアバタセプト使用ガイドライン

http://www.ryumachi-jp.com/info/guideline_ABT_100930.html

アバタセプトは，可溶性融合蛋白CTLA-4-IgG1で，上記のTNF阻害薬とは異なった特性を有するために，日本リウマチ学会・調査研究委員会の中の生物学的製剤使用ガイドライン策定小委員会が別途ガイドラインを作成した．

最後に

診療ガイドラインやリコメンデーションは，情報量が加速度的に増大していることに加えて，ガイドライン作成法自体が進歩し，質も量も飛躍的に増大した．そしてエビデンスの質がそのまま推奨度につながっていた時代は過ぎて，益と不利益，患者の価値観や医療経済的視点も加えたうえで推奨度を設定することが求められる時代に突入している．

臨床医としては，発表されるガイドラインやリコメンデーションを鵜呑みにするのではなく，それがどのような過程を経て作成されたかを理解したうえで評価し，そのうえで日常診療に応用する姿勢が必要になるであろう．

著者のCOI（conflicts of interest）開示：山中　寿；講演料（アボットジャパン，エーザイ，大塚製薬，第一三共，武田薬品工業，田辺三菱製薬，中外製薬，帝人ファーマ，ファイザー），研究費・助成金（大塚製薬，クインタイルズ・トランスナショナル・ジャパン，日本化薬，ファイザー，ユーシービージャパン），寄付金（アクテリオンファーマシューティカルズジャパン，アステラス製薬，アボットジャパン，エーザイ，MSD，大塚製薬，科研製薬，参天製薬，第一三共，大正富山医薬品，武田薬品工業，中外製薬，帝人ファーマ，ファイザー，ブリストル・マイヤーズ，ヤンセンファーマ）

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Essence of the Revised Guideline for the Management of Hyperuricemia and Gout

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Abstract

Hyperuricemia and gout are common diseases that can be treated by general and family physicians, but with the wide range of diagnosis and treatment departments that treat them, these are diseases for which guidelines are demonstrably useful. Published in 2002 by the Japanese Society of Gout and Nucleic Acid Metabolism in 2002, *the Guideline for the Management of Hyperuricemia and Gout* was subsequently revised, and in January 2010 *the Revised Guideline for the Management of Hyperuricemia and Gout* was published. While maintaining the spirit of the original guideline, the revised guideline not only fulfills the prerequisites required for formulating the current guideline but also incorporates new approaches such as the quantification of consensus levels. In addition to emphasizing that hyperuricemia has the duel aspects of being a urate deposition disease and a disease associated with lifestyle diseases, as well as the fact that all hyperuricemia patients require correction of lifestyle habits related to obesity, hypertension, and metabolic syndrome, the revised guideline covers the current evidence in detail. It is the author's sincere hope that this guideline will be utilized effectively in daily medical practice in this field.

Key words Uric acid, Recommendation level, Evidence, Consensus

Introduction

Hyperuricemia and gout are common diseases that can as a general rule be treated by general and family physicians. However, there is a wide variety of diagnosis and treatment departments that treat hyperuricemia and gout. For example, if a patient is told in a health checkup that their serum urate level is high, they see an internist; if the patient has arthritis, they see an orthopedic surgeon or rheumatologist; and if the patient has urinary lithiasis, they see an urologist. Furthermore, there are also many myths surrounding hyperuricemia and gout, with not only patients but physicians holding misconceptions in many cases. For these reasons, it can be said that these are diseases for which guidelines are demonstrably useful.

Background to the Publication of *the Revised Guideline for the Management of Hyperuricemia and Gout*

In 2000 the Japanese Society of Gout and Nucleic Acid Metabolism established the Guideline for the Management of Hyperuricemia and Gout Drafting Committee, and in 2002 published *the Guideline for the Management of Hyperuricemia and Gout*,[1] which covered in detail all of the evidence gathered at that point.

Subsequently, new drugs for treating gout were developed[2] and much evidence was also generated. The European League Against Rheumatism (EULAR) also formulated guidelines regarding gout.[3,4] Such developments increased the necessity for revision of *the Guideline for the*

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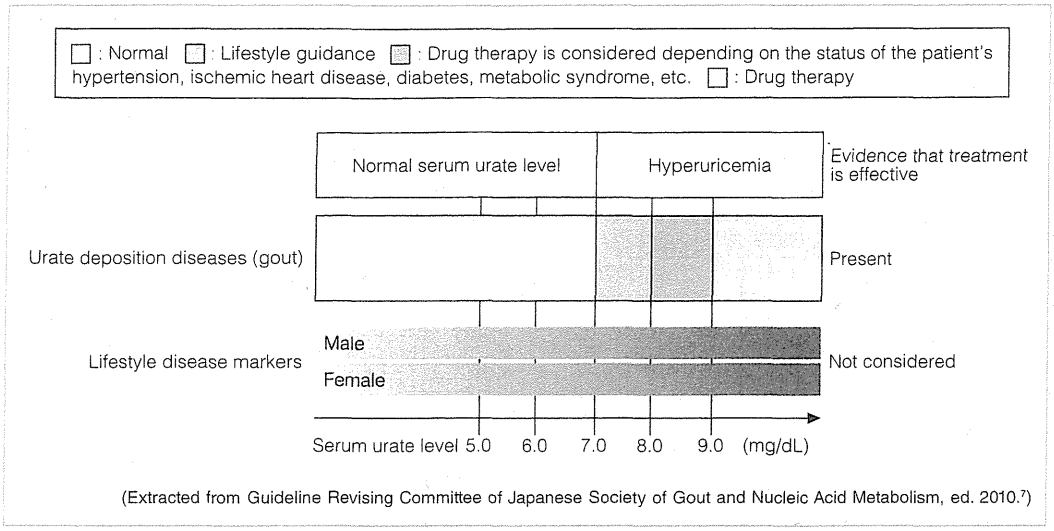


Fig. 1 Definition of hyperuricemia

Management of Hyperuricemia and Gout, and consequently the Japanese Society of Gout and Nucleic Acid Metabolism established a Guideline Revising Committee, which undertook the task of revising the guideline.

In preparing the revised guideline, guideline was formulated based on the Appraisal of Guidelines for Research and Evaluation (AGREE) checklist.[5] In addition, in this revision not only evidence levels but also consensus levels were expressed quantitatively applying the Delphi method,[6] thus incorporating the completely new approach of determining advisability for both evidence and consensus.

The Revised Guideline for the Management of Hyperuricemia and Gout[7] was published in January 2010 and a digest version was posted on the website of the Japanese Society of Gout and Nucleic Acid Metabolism (http://www.tukaku.jp/) on January 1, 2011.

Essence of *the Revised Guideline for the Management of Hyperuricemia and Gout*

The revised guideline provide statements and other information about the risks of hyperuricemia, diagnosis of hyperuricemia and gout, and treatment of hyperuricemia and gout. This paper introduces those of the statements in the guideline that are regarded as being directly applicable in daily medical practice.

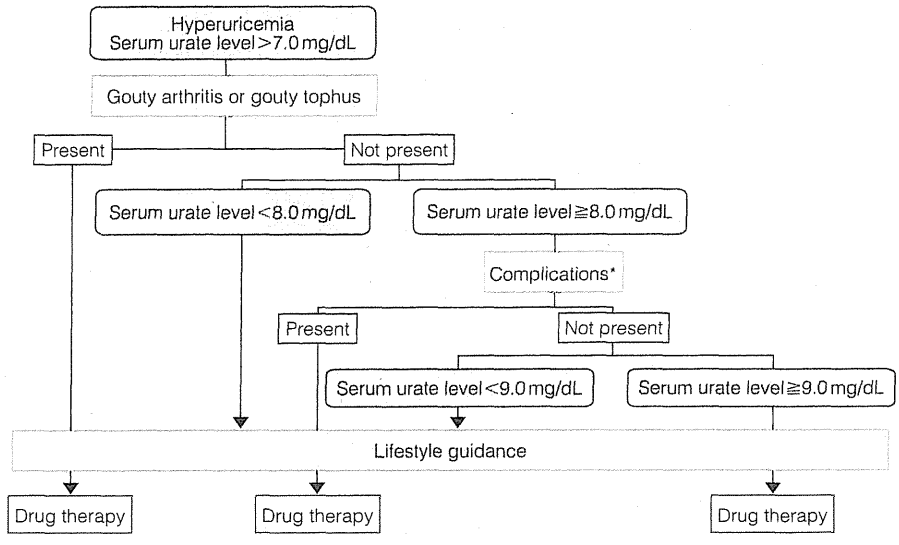
Recommendation level regarding epidemiology/diagnosis was categorized as follows:
Recommendation level A: Strong grounds for assertion
Recommendation level B: Grounds for assertion
Recommendation level C: No grounds for assertion.

Recommendation level regarding treatment was categorized as follows:
Recommendation level A: Implementation is strongly advised
Recommendation level B: Implementation is advised
Recommendation level C: Implementation may be considered.

Definition of hyperuricemia (Fig. 1)

(1) Hyperuricemia is the cause of urate deposition diseases (such as gouty arthritis and renal damage) and is defined as serum urate levels of more than 7.0 mg/dL. The disease affects people of both genders and all ages. **Recommendation level B**

(2) Amongst women, the risk of lifestyle diseases increases with rises in serum urate levels, even if serum urate levels are below 7.0 mg/dL. Testing for underlying diseases and lifestyle guidance are carried out, but uric acid-lowering drugs are not indicated. **Recommendation level B**



*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.)

(Extracted from Guideline Revising Committee of Japanese Society of Gout and Nucleic Acid Metabolism, ed. 2010.[7])

Fig. 2 Hyperuricemia treatment guidelines

The revised guideline is divided into the risks of urate deposition diseases and lifestyle disease markers. For urate deposition diseases, serum urate levels are a risk that is clearly related to disease onset, and treatment of serum urate levels reduces this risk. In contrast, for lifestyle disease markers a correlation between serum urate levels and disease onset has been shown to exist,[8] but no direct relationship has been proven and treatment has not been proven to control disease onset. Accordingly, there is also the possibility that these are simply markers, and expectations are held for future investigation.

Diagnosis of gout

(1) Gouty arthritis is arthritis caused by uric acid crystal deposits inside the joints.
(2) Acute gouty arthritis (gouty attack) appears more commonly in first metatarsophalangeal joint (MTP) and ankle joint. **Recommendation level A**
(3) For diagnosis, identification of characteristic symptoms, previous hyperuricemia, and uric acid crystals in joint fluid is important. **Recommendation level B**
(4) During a gouty attack, serum urate levels are not necessarily high. **Recommendation level B**
(5) In gouty tophus, the uric acid crystals appear granular; a fact that can applied in diagnosis. **Recommendation level A**

In the case that acute arthritis develops in the lower leg(s) of a male patient who has previously been diagnosed with hyperuricemia, there is a high possibility of gout, but differential diagnosis is necessary. Although hyperuricemia is well-known, it must be noted that during the period in which gouty arthritis is developing, serum urate levels are maintained lower than usual in many cases.

Treatment of gouty arthritis/gouty tophus

(1) In the precursory stage of a gouty attack, one tablet (0.5 mg) of colchicine is administered to prevent onset of the attack. In the case that gouty attacks occur frequently, administration of one tablet per day of colchicine ("colchicines cover") is effective. **Recommen-**

dation level B
(2) In the advanced stage of a gouty attack, non-steroid anti-inflammatory drugs (NSAID) are effective, but are administered for short periods only in comparatively large doses in order to soothe the inflammation (NSAID pulse therapy). Care must be taken with regard to the occurrence of side-effects. **Recommendation level B**
(3) In cases where NSAID cannot be used, NSAID administration is ineffective, or the patient experiences multiple occurrences of arthritis, adrenocortical steroids are administered orally. **Recommendation level A**
(4) Since fluctuating serum urate levels at the time of a gouty attack are known to exacerbate onset of the attack in many cases, as a general rule uric acid-lowering drugs are not administered during the attack. **Recommendation level B**
(5) Although extraction is also considered as a treatment for gouty tophus, drug therapy is also required in cases where surgery is performed. **Recommendation level B**

Colchicine is only effective in the precursory stage of a gouty attack; its effectiveness is markedly reduced after arthritis develops. The main treatment method for gouty arthritis is NSAID. Since fluctuating serum urate levels at the time of a gouty attack are known to exacerbate onset of the attack in many cases, administration of uric acid-lowering drugs must not commence administered during the attack. However, this rule does not apply in cases where the patient is already taking uric acid-lowering drugs on a regular basis.

Treatment of hyperuricemia (Fig. 2)

(1) What is most important in the treatment of hyperuricemia is the improvement of lifestyle habits that are related to the development of hyperuricemia and which also easily lead to the development of prognosis-related complications such as obesity, hypertension, and lipid metabolism abnormalities. **Recommendation level A**
(2) Drug therapy is indicated in cases where gouty arthritis occurs repeatedly or gouty tophus is diagnosed, and maintenance of serum urate levels of 6.0 mg/dL or lower is desirable. **Recommendation level A**
(3) Drug therapy for asymptomatic hyperuricemia is implemented when serum urate levels are 8.0 mg/dL or higher as a general indicator, but should be undertaken with caution. **Recommendation level C**

Lifestyle guidance is necessary for all hyperuricemia patients. In addition, administration of uric acid-lowering drugs is begun and continued as necessary. In such cases, serum urate levels are strictly controlled to remain at 6.0 mg/dL or lower.

There is scant evidence regarding treatment for asymptomatic hyperuricemia and consensus is also insufficient. First of all, patients undergo lifestyle guidance, and then if serum urate levels remain high, drug therapy is considered.

Treatment of hyperuricemia/gout with concomitant renal damage

(1) In cases of hyperuricemia/gout complicated by concomitant renal damage or urinary lithiasis, allopurinol is administered to lower uric acid levels. In addition, in cases complicated by renal damage, administration of allopurinol and benzbromarone in small dosages is effective. **Recommendation level B**
(2) As renal function declines, it is necessary to reduce the allopurinol dosage used. **Recommendation level B**
(3) Treatment of hyperuricemia using allopurinol is helpful in maintaining renal function in chronic kidney disease (CKD) patients. **Recommendation level B**
(4) Losartan potassium is helpful in controlling hypertension/hyperuricemia in renal transplant patients undergoing cyclosporine therapy. **Recommendation level A**
(5) Uricosuric drugs are highly useful in controlling post-renal transplant hyperuricemia following a renal transplant. **Recommendation level B**
(6) Hyperphosphatemia treatment with sevelamer hydrochloride—used with maintenance hemodialysis patients—also prevents/reduces hyperuricemia. **Recommendation level B**

Since the effectiveness of uricosuric drugs declines in cases where the patient has moderate to high renal damage, allopurinol is the drug of

first choice, but care is necessary as allopurinol is a renal excretory and can cause serious side-effects. Hyperuricemia treatment using allopurinol is gaining attention due to its usefulness in maintaining renal function in CKD patients.

Treatment of hyperuricemia/gout with concomitant urinary lithiasis

(1) Guidance concerning water intake aims to ensure that patients drink 2,000 mL/day of water or more. **Recommendation level B**
(2) Allopurinol is the drug of first choice for the treatment of hyperuricemia complicated by concomitant urinary lithiasis. **Recommendation level B**
(3) Because uricosuric drugs stimulate the formation of urate stones, as a general rule they are not used in the treatment of hyperuricemia cases complicated by concomitant urinary lithiasis. **Recommendation level B**
(4) Using mainly citric acid formulations, the aim of urine alkalinization is to maintain urine ph between 6.0 and 7.0. Diet therapy, such as purine intake limitations, also needs to be implemented concurrently. **Recommendation level B**
(5) Allopurinol and urine alkalinization drugs are effective in preventing the reoccurrence of calcium oxalate stones associated with hyperuricosuria. **Recommendation level A**
(6) The main treatment for urate stones is extracorporeal shock wave lithotripsy (ESWL), but stone dissolution therapy using urine alkalinization drugs or allopurinol is also an option. **Recommendation level B**

Amongst hyperuricemia/gout patients, there is a high frequency of urinary lithiasis complications, and attention should be paid to urinary tract management. Drinking water is especially important and has the effect of preventing increases in serum urate levels due to dehydration.

Treatment of hyperuricemia/gout with concomitant hypertension

(1) For hyperuricemia patients with hypertension complications, first of all lifestyle guidance is carried out with the aim of "avoiding risks to organs overall" by simultaneously improving lifestyle habits related to the onset of hyperuricemia. **Recommendation level B**
(2) Drug therapy prioritizes blood pressure management, and it is desirable to give priority as far as possible to the use of antihypertensive drugs that do not negatively impact uric acid metabolism. **Recommendation level B**
(3) Even when lifestyle guidance and antihypertensive drugs preferable for uric acid metabolism are used, commencing administration of uric acid-lowering drugs is considered in cases where serum urate levels are 8.0 mg/dL or higher. It is desirable to maintain serum urate levels during treatment to 6.0 mg/dL or lower. **Recommendation level C**
(4) Selection of uric acid-lowering drugs is made based on disease pattern classification, and therapeutic agents and dosages are carefully decided based on the degree of renal damage and presence/absence of hepatic damage. In addition, urine pH is measured and concomitant use of urine alkalinization drugs is also considered. **Recommendation level C**

Hypertension is a highly frequent complication for patients with hyperuricemia/gout, and appropriate management from an early stage is necessary due to the effect on long-term prognosis. Although some antihypertensive drugs raise serum urate levels, losartan potassium, captopril, and enalapril are effective in treating hyperuricemia/gout complicated by hypertension because of their combined hypotensive and uricosuric effects.

Treatment of hyperuricemia/gout with concomitant hyperlipidemia

(1) In addition to treating hyperuricemia, therapy also aims to treat hyperlipidemia—which is a factor in arteriosclerotic disease—and alleviate the arteriosclerotic disease. **Recommendation level A**
(2) Diagnosis is made in accordance with the diagnostic criteria stipulated in *the Arteriosclerotic Disease Prevention Guidelines* (2007). That is, a diagnosis of hyperlipidemia is made when the patient has LDL-hypercholesterolemia (LDL-cholesterol≧140 mg/dL), HDL-hypocholesterolaemia (HDL-cholesterol <40 mg/dL), or hypertriglyceridemia (triglycerides≧150 mg/dL). **Recommendation level A**
(3) Treatment of hyperlipidemia complicating

hyperuricemia/gout is carried out in accordance with *the Arteriosclerotic Disease Prevention Guidelines* (2007). **Recommendation level A**
(4) Some drugs used to treat hyperlipidemia also have an effect on serum urate levels, and so these are considered. In particular, fenofibrate is an effective medicinal agent in cases complicated by hypertriglyceridemia and hyperuricemia, especially hyperuricemia causing a decreased uricosuric effect. **Recommendation level A**

Hyperlipidemia is a highly frequent complication for patients with hyperuricemia/gout, and appropriate management from an early stage is necessary due to the effect on long-term prognosis. Because fenofibrate has a uricosuric effect, it is useful in the treatment of patients with hyperuricemia/gout complicated by hyperlipidemia.

Lifestyle guidance for patients with hyperuricemia/gout

(1) Hyperuricemia and gout are representative lifestyle diseases. Lifestyle guidance is a non-drug therapy aimed at correcting lifestyle habits and plays an important role in treatment regardless of whether or not drug therapy is implemented. **Recommendation level B**
(2) Lifestyle guidance for hyperuricemia/gout patients centers on diet therapy, limitation of alcohol intake, and encouragement of exercise, and reducing obesity is expected to have the effect of lowering serum urate levels. **Recommendation level B**
(3) In diet therapy, patients are advised about correct energy intake, limitations on excessive purine and fructose intake, and drinking sufficient water. **Recommendation level B**
(4) Physical activity (exercise) can be encouraged to improve various pathological conditions of metabolic syndrome. **Recommendation level C**

In diet therapy for hyperuricemia/gout patients, if we consider obesity and metabolic syndrome, which complicate hyperuricemia/gout with a high frequency, rather than focusing on purine limitation, quantitative limitation is more important than qualitative limitation. First of all, patients receive guidance on how to reduce total energy intake amounts. If a patient's weight decreases, their serum urate levels will decrease. Moreover, in cases where lifestyle guidance is only minimally successful and drug therapy is implemented, correct lifestyle habits should be continued.

Conclusion

The Revised Guideline for the Management of Hyperuricemia and Gout—which, in addition to continuing the spirit of the original guideline, fulfills the prerequisites required for formulating the current guideline as well as incorporates new approaches such as quantifying consensus levels—was released in January 2010. It is the author's sincere hope that this guideline will be utilized effectively in daily medical practice in this field.

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REVIEW ARTICLE

Management of rheumatoid arthritis: the 2012 perspective

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Abstract Management of rheumatoid arthritis (RA) has improved over the last 10 years. These changes have been monitored in the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) observational cohort, and clinical remission has become a realistic goal. However, we should recognize that the ultimate goal of treatment is to improve long-term outcomes. These improvements have been achieved not only by new drugs, but also by the overall approach toward treating patients. Biologics in RA have been successful; however, safety concerns and pharmacoeconomical issues are still debated. Protein kinase inhibitors have been developed, and can be called "molecular-targeting antirheumatic drugs" (MTARDs), as opposed to "disease-modifying antirheumatic drugs." In comparison with biologics, oral MTARDs should be less expensive; however, their safety profile should be confirmed. Considering the limitations of randomized trials, it is encouraged to conduct studies based on daily practice. It is time to consider the application of the evidence generated from "our" patients to patients in daily practice, namely institute-based medicine as opposed to evidence-based medicine, of which "IORRA-based medicine" would be representative. Finally, there remains much for us rheumatologists to do for our patients, including patient-perspective approaches.

Keywords Outcome · Observational cohort · Biologics · MTARDs · Patient perspective

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What have we achieved since 2000?

The readers of *Modern Rheumatology* know that, over the last 10 years, care of patients with rheumatoid arthritis (RA) has seen impressive improvements. New drugs with novel modes of action have led to improvements not only in signs and symptoms, but also in long-term outcomes, including joint destruction and disability. Therefore, the goal of RA treatment has changed from improving outcomes over the short term to outcomes over the long term. The proposal that there should be a paradigm shift from "care to cure" has become realistic.

The changes generated in the last 10 years have been carefully monitored since 2000 in the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) observational cohort [1, 2]. We previously reported that disease activity in the IORRA cohort improved significantly from 2000 to 2007 [3]; subsequently, there has been constant improvement along with the changes in the drugs employed for therapy (Fig. 1). Clinical remission has become a realistic goal. By any of the 2010 criteria for remission proposed by the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR), the number of patients in remission has increased [4, 5] (Fig. 2). This progress has been the result of the increased use of methotrexate and biologics. Based on data mainly from IORRA, the maximum dose of methotrexate has been raised [6, 7], and this will lead to better patient outcomes over the next decade. It is amazing that changes in disease control have resulted from the use of nonsteroidal anti-inflammatory drugs as well as gastrointestinal medications (Fig. 3).

An IORRA study conducted in the prebiologic era found a standardized mortality ratio (SMR) of 1.46-1.90, which was consistent with findings from Western countries [8]. Advances in drug therapy may improve the survival of RA

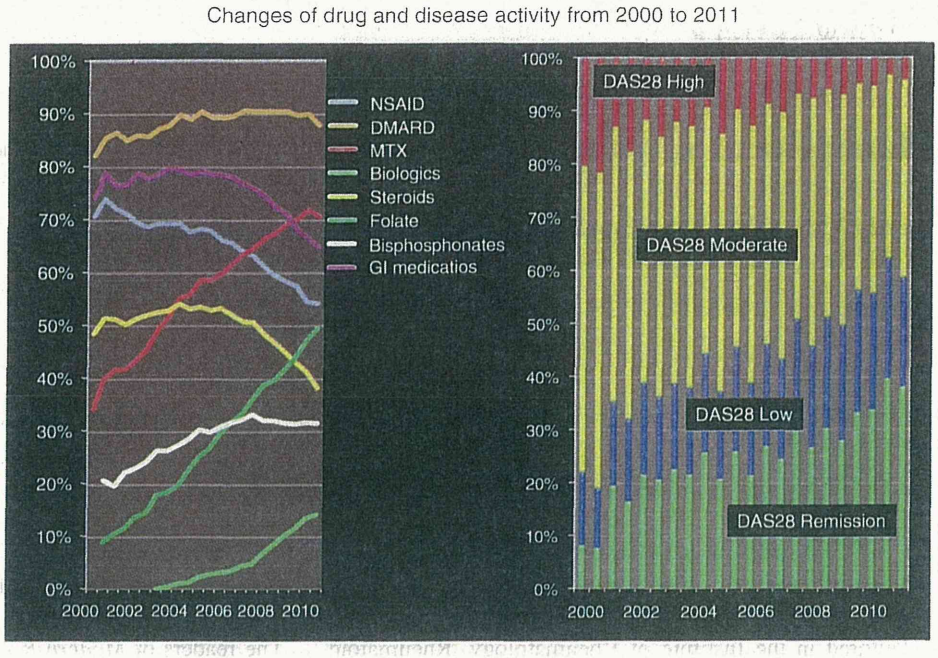

Fig. 1 Changes of drug and disease activity from 2000 to 2011. Changes of drug use and disease activity of RA patients in the IORRA cohort from 2000 to 2011 are shown. Disease activity was categorized by DAS28 according to the standard method

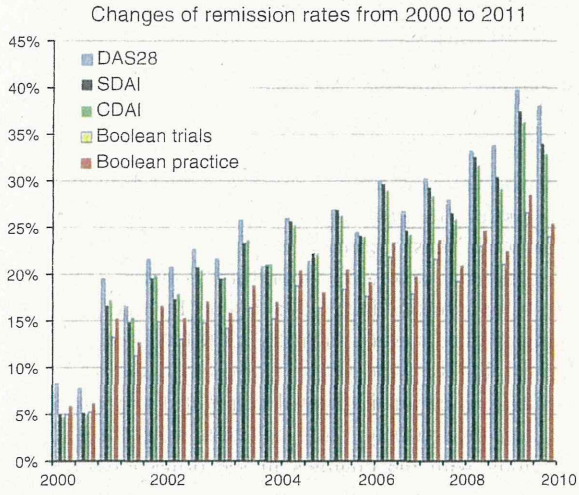

Fig. 2 Changes of remission rates from 2000 to 2011, defined by 5 methods including DAS28, simplified disease activity index (SDAI), clinical disease activity index (CDAI), Boolean trials, and Boolean practice. Definition of remission is based on each criterion

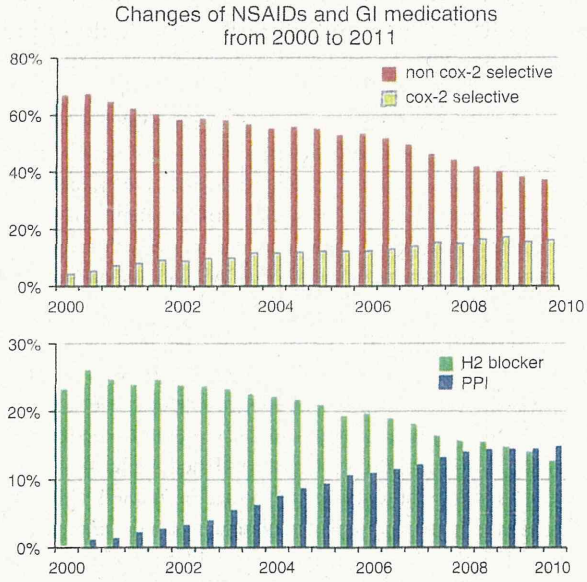

Fig. 3 Changes of use of NSAIDs (*upper column*) and gastrointestinal (GI) medications (*lower column*) from 2000 to 2011. NSAIDs were categorized by cyclooxygenase-2 (COX-2) selectivity as COX-2 selective (celecoxib, meloxicam, and etodolac) or non-COX-2 selective (others). Categorizations of proton pomp inhibitor (PPI) and H2 blocker are based on label information

patients [9]. We recently undertook a nationwide study to estimate the mortality rate of RA patients treated using biologics (Nakajima A, et al. submitted); our findings need confirmation by a more precise study. It is extremely important to recognize that the ultimate goal of the treatment of patients with RA is to improve long-term outcomes, including mortality and quality-adjusted life years (QALYs) [10].

We would like to emphasize that improvements in patient management have been achieved not only by new drugs. It is apparent that new drugs initiated these changes, but in addition, major improvements have been achieved in the overall approach toward treating patients with RA. The establishment of treatment recommendations [11, 12] for management of RA, and the introduction of new criteria for classification [13] and remission [4, 5], are important

platforms for introducing novel treatments into daily practice.

We previously reported several findings that support the concept that strict control of disease activity by maintaining the disease activity score using 28 joint count (DAS28) at a low value can inhibit the progression of disability in patients with RA [3, 14]. This target-driven therapeutic strategy ("treat to target") has become familiar as the T2T movement since recommendations for achieving optimal outcomes were published in 2010 [15]; we first reported on use of "treat to target" in 2007 [3].

Progress in the technology of imaging modalities, including ultrasound and magnetic resonance imaging (MRI), has led to increased accuracy of diagnosis. As suggested by the new classification criteria for polymyalgia rheumatica [16], the addition of ultrasound information will increase the sensitivity and specificity of the diagnosis of early rheumatoid arthritis. Although there remains the problem of feasibility, ultrasound should be widely implemented for routine care of RA patients [17]. These diagnostic strategies were established based on the results of several clinical studies, predominantly randomized controlled trials (RCTs) [18]. Comparing the study patients in RCTs with patients in daily practice is debatable, which we return to later in this review.

When we consider the changes that have occurred over the last 10 years, we can see that the strategies of RA treatment have changed dramatically as a result of the productive collaboration of academic expertise and innovative companies.

The future of the biologic era

Everyone can agree that molecular targeting is one of the best ways to control disease activity for a disease in which the target molecule has been identified. RA is phenotypically a quite heterogeneous disease, but the pathophysiology is quite uniform. Although many molecules are involved in the pathogenesis of RA, there are only a few key molecules that can be targeted for treatment. Tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) have been most successfully targeted, and the introduction of monoclonal antibodies and receptor-fusion proteins has successfully led to suppression of RA disease activity [19, 20].

There are several other candidate molecules that may be targeted for RA treatment, including CD86, CD20, CD22, and B cell activating factor (BAFF), which are functional surface molecules of T cells or B cells; and IL-17 and IL-12/23, which are proinflammatory cytokines [21, 22]. Antibodies and/or fusion proteins with activity against those molecules have been developed and are in clinical trials. In the near future, we may have more than 10 effective drugs for treatment of RA. The efficacy and safety profiles of these biologics may differ according to their target molecules, but an essential characteristic of these drugs is their ability to suppress joint destruction and improve long-term outcomes. Improvement in the signs and symptoms of each RA patient is a minimum requirement, but will not be sufficient for a candidate drug to become a useful therapeutic option.

It should be recognized that these macromolecular drugs cannot cross cell membranes, and are active extracellularly. Therefore, these biologics are quite safe with regard to hepatotoxicity, nephrotoxicity, and hematotoxicity. Concerns regarding the safety of biologics focus on the immunogenic reactions against exogenous proteins and the results of the suppression of target molecules. Preclinical and clinical data accumulated over the last 10 years have demonstrated that hypersensitivity to these macromolecules occurs at a tolerable level, and is manageable in daily practice. However, suppression of target molecules is a major problem affecting the safety profiles of these biologics; For example, TNF-α is part of the endogenous line of defense against tuberculosis infection, and suppression of TNF-α has resulted in increases in reactivation of occult tuberculosis infection [23]. Thus, it very important to predict the possible side-effects of any biologic by considering the role of its target molecule. However, all of the target molecules of the biologics used to treat RA are associated with the immune system of the host, and therefore susceptibility to infection is an unavoidable issue. Efforts have been made to identify patients highly susceptible to infection, so that an effective prophylactic regimen can be instituted; however, prevention of opportunistic infections, including pneumocystis pneumonia, remains an important concern [24].

Use of biologics to treat RA is a pharmacoeconomical issue. These macromolecules are quite expensive compared with other drug classes, because they are produced using advanced technology. The outpatient costs incurred from 2000 to 2007 for 8,982 RA patients (34,839 patient-years) enrolled in the IORRA study were evaluated. The mean annual outpatient cost increased from 287,626 JPY in 2000 to 366,964 JPY in 2007 (+27.6 %). The cost of medications and injections over those 7.5 years increased 39.0 and 1215 %, respectively. Costs increased in association with aging, increased DAS28 values, and increased Japanese Health Assessment Questionnaire (J-HAQ) scores. Levels of disability and use of biologics were the most significant factors associated with cost increases. Outpatient care costs for patients with RA also increased over the last 7.5-year period, especially after the introduction of biologics [25].

Extensive pharmacoeconomical analysis has demonstrated that biologics are cost-effective when work

productivity is taken into consideration, but cost is an obvious barrier to RA patients who have lost their job because of their disease. Our recent data have shown that biologics are most cost-effective when used in patients with early RA and with moderate disability (J-HAQ = 1.0–1.5) (Tanaka E, et al. submitted). In the effort to improve patient quality of life (QOL), this use of biologics for earlier disease is needed for effective utilization of limited medical resources.

Another promising approach for improving the cost benefits of biologics is the development of generic biologics, also known as biosimilar products [26]. Clinical studies of these biosimilar products are now being conducted in many countries, including Japan.

Antirheumatic drugs: DMARD to MTARD

Control of disease activity in RA had its origins in the empirical use of gold compounds in clinical practice, and was not the result of scientific evaluations. Gold compounds belong to the class of drugs called disease-modifying antirheumatic drugs (DMARDs). The target molecules of DMARDs, including gold compounds, D-penicillamine, sulfasalazine, bucillamine, and actarit, have not been clearly identified, but the targets of methotrexate, leflunomide, mizoribine, and tacrolimus have been well defined. Now there is a new class of drugs, including protein kinase inhibitors, which target unique molecules that regulate cell functions. Many of these drugs have been classified as immunosuppressive drugs. We propose a tentative generation-based classification of these immunosuppressive drugs according to when they were discovered (Table 1).

The molecular targets of the drugs in the 1st to 3rd generations were identified after discovery of the drug; however, the 4th generation of immunosuppressive drugs is a novel class of antirheumatic drugs that have been developed based on molecular targets. Thus, we would like to propose the designation "molecular-targeting antirheumatic drugs" (MTARDs), as opposed to "disease-modifying antirheumatic drugs" (DMARDs).

Thus far, five oral compounds including kinase inhibitors (tofacitinib, fostamatinib, VX-509), an S1P lyase inhibitor (LX 3305), and a chemokine receptor-1 antagonist (CCX354-C) have been developed [27, 28]. Because there are many target molecules involved in regulating cell function in the immune system, many novel drugs classified as MTARDs should be discovered (Table 2).

MTARDs are small-molecule compounds with high specificity for the target molecule. In comparison with biologics, MTARDs are administered orally, and their production should be less expensive. Therefore, if they are noninferior to DMARDs, MTARDs would provide advantages over biologics, since biologics are not administered orally and are expensive.

Table 1 Immunosuppressants

Generation	Mode of action	Drugs
1st	DNA damaging agents	Cyclophosphamide, alkylating agents
2nd	Purine/pyrimidine antimetabolites	Methotrexate, leflunomide, mizoribine, azathioprine
3rd	Calcineurin inhibitors	Cyclosporine, tacrolimus
4th	Protein kinase inhibitors	Tofacitinib, fostamatinib

Table 2 Comparison of DMARDs and MTARDs

Class		Definition	Drugs
DMARDs	Disease-modifying antirheumatic drugs	Target molecule is unknown, or was identified after drug development	Gold, D-penicillamine, sulfasalazine, bucillamine, methotrexate, leflunomide, tacrolimus, etc.
MTARDs	Molecular-targeting antirheumatic drugs	Drug was developed directly to target the molecule	Tofacitinib, fostamatinib, etc.

The safety profile of MTARDs is a concern. MTARD actions occur intracellularly, and MTARDs must cross the cell membrane. Thus, cytotoxicity may be inevitable if MTARDs must be administered in high concentrations. In addition, regulation of intracellular protein kinases, the target molecules, is thought to be sensitive to concentration; therefore, changes in levels of protein kinases may lead to side-effects [29]. Since kinases are phosphotransferases, these kinase-inhibiting drugs will inhibit adenosine triphosphate (ATP) binding at the catalytic sites of kinases [30], and may nonspecifically inhibit ATP binding. In vivo and in vitro experiments should be performed for clarification. The results of phase 1–3 clinical trials of the first MTARD, tofacitinib, indicate that it was relatively well tolerated, and it has been submitted for approval in the USA, European Union, and Japan [31].

Importance of practice-based clinical studies

As mentioned earlier in this review, there are many guidelines and recommendations regarding therapeutic strategies for daily practice that have been established, including the most recent ACR recommendation [12]; however, it is important that these have been established based on the results of many clinical studies, including

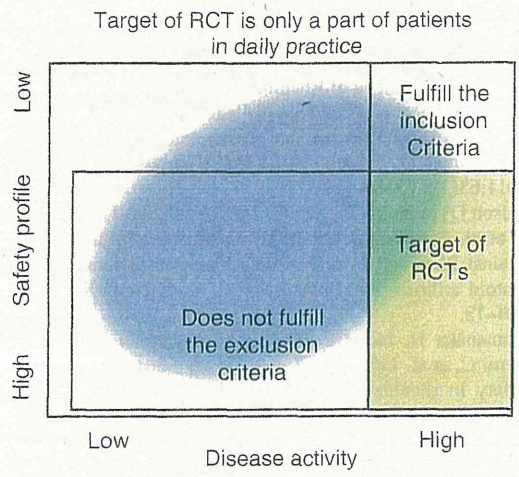

Fig. 4 The target of a RCT is only a part of the patients in daily practice. The target population of most randomized controlled trials (RCTs) is limited by the inclusion and exclusion criteria of the study. In most RCTs for RA, patient inclusion is dependent on disease activity and exclusion is dependent on safety profiles

many RCTs. RCTs are quite appropriate for determining the efficacy and safety profile of a drug or therapeutic strategy, but the population of study patients is usually restricted because of the study inclusion and exclusion criteria (Fig. 3).

It has been argued that only a small fraction of patients in daily practice would satisfy the inclusion and exclusion criteria of the clinical studies of biologics [17]; therefore, the therapeutic strategies established by clinical studies are acceptable but not ideal for implementation in daily practice. As Professor Furst has commented, "Well-designed clinical studies and observational cohorts, we need them both" [32]. Many RCTs have been conducted by pharmaceutical companies, but it is extremely difficult for a company to organize and maintain an observational cohort based on daily practice. There are many registries and observational cohorts of RA patients, including IORRA, CORRONA [33], NOR [34], and SRR [35]. We believe that consideration should be given to basing the guidelines and recommendations for RA therapeutic strategies on these practice-oriented databases. In addition, we would like to encourage clinical studies based on all the patients seen in daily practice (Fig. 4).

One of the pitfalls of evidence-based medicine (EBM) has been the application of the results of clinical studies that were conducted under medical conditions different from those of the patients in our daily practice. Even if the essential baseline characteristics are similar, the study patients might be of different ethnicities, with different comorbid diseases, concomitant medications, methotrexate doses, financial support, or medical insurance. These are the limitations of EBM, and we have to think about the application of evidence generated from "our" patients to patients in daily practice. We have established a large cohort of IORRA patients with RA, and various evidence-based findings can be generated by appropriate analyses; therefore, it is possible to apply the data from the IORRA cohort to our patients in IORRA. We call this approach "institute-based medicine" (IBM) or "IORRA-based medicine" (also IBM). It may not be feasible to apply this concept to all patients in all clinical situations, but we think that we have to try to improve the quality of evidence by considering the medical circumstances of each patient.

Thoughts on a patient-friendly program

The aim of RA treatment is the well-being of RA patients. Patient self-care is needed to prevent disease progression; however, RA is essentially not a lifestyle-related disease where patient effort yields a better outcome. Thus, medical professionals, including rheumatologists, must modify the course of the disease so that it leads to the best outcome. If patients are not educated about their disease, or are depressed by a poor disease outcome, effective treatment cannot be delivered. As treatment goals have become more optimistic over the years since the introduction of rigorous control of disease activity, there is also a tendency to administer stronger immunosuppression to patients. Both patients and health professionals have to be acutely aware of the early signs and symptoms of adverse events, including opportunistic infections, since anticytokine therapy may sometimes mask those signs [36].

Considering these issues, our IORRA cohort has been established essentially based on information from patients [1–3]. OMERACT has been conducting workshops on patients' perspectives for over 10 years [37], which has led to a recently published definition of RA remission from the patient perspective [38]. Thus, patient education and participation has become increasingly important. As a part of the T2T program, the patient version of the T2T program has been published [37] and translated into many languages, including Japanese. Furthermore, product-specific campaigns that focus on patients who are prescribed a specific drug have been developed, with an aim of specifying the important issues of care in daily life. These are welcome developments in the management of RA and may lead to better patient outcomes. Thus, rheumatologists must share their experience with their patients.

Future perspectives

It has been proposed that medicine of the future should be described by the 4 Ps: predictive, personalized, preventive,