（報告様式４）

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I. 基本情報

事　業　名：

（日本語）免疫アレルギー疾患等実用化研究事業（免疫アレルギー疾患実用化研究分野）

（英　語）Practical Research Project for Allergic Diseases and Immunology (Research on Allergic Diseases and Immunology)

研究開発課題名：

（日本語）関節リウマチの「ドラッグホリデー」と関節破壊「ゼロ」を目指す治療法の確立に関する研究

（英 語）Practical research project to establish treatment strategies for “drug-holiday” and “joint damage-zero” in patients with rheumatoid arthritis

研究開発担当者（日本語）産業医科大学医学部第１内科学講座　教授　田中良哉

所属 役職 氏名：

（英 語）Yoshiya Tanaka, Professor and Chairman, The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan

実 施 期 間：　平成２６年４月１日　～　平成２９年３月３１日

分担研究（日本語）関節リウマチ滑膜炎に対する画像検査に関する研究

開発課題名：

（英　語）Imaging study of rheumatoid synovitis

研究開発分担者（日本語）北海道大学大学院医学研究科免疫・代謝内科学分野・教授・渥美　達也

所属 役職 氏名：

（英　語）Hokkaido University Graduate School of Medicine Faculty of Medicine　Department of Rheumatology, Endocrinology and Nephrology

分担研究（日本語）関節リウマチの臨床的アウトカムに関わる背景因子の探索

開発課題名：

（英　語）Research on the effect of patients’background on clinical outcome of rheumatoid arthritis

研究開発分担者（日本語）埼玉医科大学総合医療センター　リウマチ膠原病内科　教授　天野 宏一
所属 役職 氏名：
（英　語）Saitama Medical Center, Saitama Medical University, Department of Rheumatology and Clinical Immunology, Professor Kochi Amano

分担研究（日本語）関節超音波を用いた関節リウマチの生物学的製剤（バイオ）フリー寛解維持に関する研究
開発課題名：
（英 語）Exploratory study of sustained clinical remission by musculoskeletal ultrasound in rheumatoid arthritis patients after discontinuation with bDMARDs

研究開発分担者（日本語）長崎大学大学院医歯薬学総合研究科先進予防医学講座　教授　川上　純
所属 役職 氏名：
（英　語）Atsushi Kawakami, Professor and Chairman Department of Immunology and Rheumatology, Unit of Advanced Preventive Medical Sciences, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences

分担研究（日本語）寛解リウマチ患者に残存する関節炎惹起能を評価するバイオマーカーの探索
開発課題名：
（英　語）Identification of biomarkers to predict the flare of disease activity in rheumatoid arthritis

研究開発分担者（日本語）東京医科歯科大学　膠原病・リウマチ内科　教授　上阪　等
所属 役職 氏名：
（英　語）Hitoshi Kohsaka, Department of Rheumatology, Tokyo Medical and Dental University

分担研究（日本語）MRI 画像による生物学的製剤の導入および休薬のための予測基準の検討
開発課題名：
（英　語）Prediction criteria for introduction or withdrawal of biological DMARDs by MRI imaging

研究開発分担者（日本語）筑波大学　医学医療系 膠原病･リウマチ･アレルギー内科　教授 住田　孝之
所属 役職 氏名：
（英　語）Takayuki Sumida, Professor, Department of Internal Medicine, Faculty of Medicine, University of Tsukuba

分担研究（日本語）MTX-PG と IL-6 を用いた関節破壊ゼロと薬剤フリー寛解維持の予測因子に関する研究
開発課題名：
（英　語）Investigation of prediction factors to maintenance of zero joint destruction and drug-free remission with MTX-PG and IL-6

研究開発分担者（日本語）慶應義塾大学医学部リウマチ膠原病内科 教授　竹内勤
所属 役職 氏名：
（英　語）Keio University School of Medicine, Department of Internal Medicine, Division of Rheumatology

分担研究（日本語）薬剤「フリー」寛解の予測因子としての血中 IL-6 の有用性の検討
開発課題名：
（英　語）Validation of serum IL-6 level as a predictive biomarker for sustained drug-free remission in rheumatoid arthritis.

研究開発分担者（日本語）東京医科大学医学総合研究所　難病分子制御学部門　特任教授 西本　憲弘
所属 役職 氏名：
（英　語）Norihiro Nishimoto. Department of Molecular Regulation for Intractable Diseases Institute of Medical Science,Tokyo Medical University,Professor,

分担研究（日本語）バイオフリー寛解を維持しえた関節リウマチ患者の遺伝学的・血清学的背景の検討
開発課題名：
（英　語）Genetic and Serological characteristics of rheumatoid arthritis patients who achieved bio-free remission.

研究開発分担者（日本語）京都大学大学院医学研究科内科学講座臨床免疫学　教授　三森経世
所属 役職 氏名：
（英　語）Tsuneyo Mimori, Professor of Kyoto University Graduate School of Medicine, Department of Rheumatology and Clinical Immunology
分担研究（日本語）RA 患者の末梢血リンパ球における遺伝子発現に注目した寛解の条件とその誘導
開発課題名：
（英　語）Analysis and induction of clinical remission based on gene expressions of peripheral blood lymphocytes in rheumatoid arthritis.

研究開発分担者（日本語）東京大学医学部アレルギー・リウマチ内科 教授　山本一彦
所属 役職 氏名：
（英　語）Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo. Professor　Kazuhiko Yamamoto

II. 成果の概要（総括研究報告）

・ 研究開発代表者による報告の場合

関節リウマチ（RA）に伴う多発関節炎や進行性関節破壊は、多大なる社会的損失を生じてきた。一方、MTX や生物学的製剤の使用により臨床的寛解や構造的寛解が可能となった。しかし、生物学的製剤の長期連用による安全性や経済性は国内外で喫緊の課題であるが、治療薬の減量や中止に関するガイドラインは国内外共に存在しない。本研究では、RA 患者の「ドラッグホリデー」を目指す治療ガイドラインの確立と検証 [" FREE-J" 試験 (UMIN000014856)]を目的として研究を行なった。また、発症早期から保険診療内の強化療法により関節破壊を『ゼロ』にすることを目指した策定した治療指針を検証し、関節破壊を生じない治療法の確立を目的とした研究 ["ZERO-J"試験（UMIN000001281）]を実施した。

FREE-J 試験では、MTX と生物学的製剤にて治療し、DAS28(ESR)寛解を 2 回連続満たした症例を、治療継続、MTX 半減、MTX 中止、生物学的製剤減量、生物学的製剤中止の 5 群に分け、１年後の DAS28 寛解を主要評価項目とした。ZERO-J 試験では、MTX 未使用の早期の症例を登録し、十分量の MTX を 3 ヶ月投与後、TNF 阻害薬を 1 年間投与（T 群）、MTX で 1 年間治療を継続（M 群）、MTX で寛解、低疾患活動性を満たした high responder (HR) 群として 1 年間経過観察する。主要評価項目は、開始 1 年後の総 Sharp 値変動（ΔmTSS）で示した関節破壊の進行とした。

FREE-J 試験では、2016 年 11 月現在、参加 13 施設で 385 症例が登録された。平均年齢 57.7 歳、罹病期間 104 月、MTX 10.6 mg/W、TNF 阻害薬 79%、生物学的製剤平均治療期間 36 ヶ月、生物学的製剤による平均寛解維持期間 21 ヶ月であった。治療継続、MTX 半減、MTX 中止、生物学的製剤減量、生物学的製剤中止は、MTX 減量が多く、MTX 中止は稀であった。今後、MTX や生物学的製剤の減量や中止を検証するとともに、探索的研究によりドラッグホリデーを可能とする患者を識別する治療戦略を構築する必要がある。

ZERO-J 試験では、2015 年度には早期 RA 患者 162 例が登録され、平均罹病期間 7.4 月、MTX 治療開始時点で DAS28 は 4.8、SDAI は 20.4 であった。登録後 3 か月後に MTX は 12.0ｍｇ/週まで増量され、DAS28:3.7、SDAI: 12.2 まで改善し、高反応性群、TNF 治療群、MTX 併用群に振り分けられた。その結果、① 早期 RA 患者の 6 割は MTX で臨床的にも構造的にも制御可能、② 治療前の疾患活動性が低～中等度の患者は MTX のみでコントロール可能、③ MTX 治療 3 ヶ月に中～高疾患活動性の患者は関節破壊が進行する可能性が高く、生物学的製剤の選択を考慮すべきであるとの結果が得られ、生物学的製剤の無駄な使用を回避できる可能性も示唆された。

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammation and joint destruction that causes significant morbidity and mortality. Polyarthritis and progressive joint destruction associated RA have often resulted in loss of quality of life and a great social and economical loss. However, the combined use of methotrexate (MTX) and biological disease-modifying anti-rheumatic drugs (bDMARDs) targeting TNF has revolutionized treatment of RA, producing significant improvements in clinical, structural and functional outcomes that were not previously observed. By the appropriate treatments, clinical remission is perceived as an appropriate and realistic primary goal in many patients, and its maintenance leads to structural and functional remission.

After sustained remission, discontinuation of bDMARDs without disease flare has been emerging as an important theme from the risk-benefit point of view as well as economic burdens. However, there are no guidelines on reducing or stopping therapeutic drugs. In this study, research was conducted with the aim of

establishing and verifying therapeutic guidelines aiming at "drug holiday" of RA patients ["FREE-J" test (UMIN000014856)]. In the FREE-J trial, patients treated with MTX and bDMARDs and having DAS28 (ESR) remission twice consecutively, were divided to 5 groups; treatment continuation, dose reduction of MTX, discontinuation of MTX, dose reduction of bDMARDs and discontinuation of bDMARDs and the primary endpoint was DAS28-remission after 1 year. In the FREE-J trial, 385 cases were registered at 13 participating sites. Average age 57.7 years, disease duration 104 months, MTX 10.6 mg/W, prior use of TNF inhibitors 79%, average treatment duration with bDMARDs 36 months, average time to maintain remission by bDAMRDs 21 months. It is necessary to verify the dose reduction and discontinuation of MTX and bDMARDs, and to construct a therapeutic strategy to identify patients who can make drug holiday through this exploratory research.

Meanwhile, a study aimed at establishing therapeutic guidelines to make joint destruction "zero" by appropriate and intensive intervention from just after the diagnosis of RA was carried out ["ZERO- J "test (UMIN 000001281)]. In the ZERO-J study, RA patients with MTX-naïve were enrolled and were treated with adequate dose of MTX for 3 months. If patients fulfilled the JCR guideline for the use of bDMARD, namely DAS28>3.2 or progress in joint damage, patients were treated with either TNF-inhibitors (T group) or csDMARDs including MTX (M group) for 1 year and if did not fulfill the guideline, MTX were maintained as a high responder group (HR group) for 1 year. The primary endpoint was yearly progression of modified total Sharp score (ΔmTSS) at 1 year after the grouping. 162 early RA patients were enrolled in the study, with mean disease duration of 7.4 months, DAS28 of 4.8 and SDAI of 20.4 at the start of MTX treatment. Three months after enrollment, MTX was increased to 12.0 mg/week, average disease activities were improved to DAS28: 3.7, SDAI: 12.2. The patients were distributed to 3 groups at 3 months after the enrollment. As results, (1) 60% of patients with early stage RA can be clinically and structurally controlled by adequate dose of MTX alone, (2) patients with low to moderate disease activity before treatment can be controlled with MTX alone, (3) Patients with moderate to high disease activity despite adequate MTX therapy for 3 months are more likely to develop joint destruction and bDMARDs should be considered. From these strategies, joint damage as well as wasteful use of bDMARDs can be avoided.

III. 成果の外部への発表

（１） 学会誌・雑誌等における論文一覧（国内誌　5　件、国際誌　51　件）

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