

令和 6 年 6 月 20 日現在

機関番号：10101

研究種目：基盤研究(C)（一般）

研究期間：2020～2023

課題番号：20K11597

研究課題名（和文）Effects of fish consumption on clinical response to targeted therapies in Japanese and Spanish patients with rheumatoid arthritis

研究課題名（英文）Effects of fish consumption on clinical response to targeted therapies in Japanese and Spanish patients with rheumatoid arthritis

研究代表者

Amengual Olga (Amengual, Olga)

北海道大学・医学研究院・講師

研究者番号：10636939

交付決定額（研究期間全体）：（直接経費） 3,300,000円

研究成果の概要（和文）：慢性炎症疾患である関節リウマチ（RA）の経過に食事習慣が影響を及ぼす可能性がある。本研究は、日本とスペインのRA患者を対象に、n-3系多価不飽和脂肪酸（PUFA）を豊富に含む魚の摂取が治療反応に及ぼす影響があるかどうかを調査することを目的とした。後ろ向き観察研究では、日本人では週1回以上のn-3系PUFAを多く含む魚の摂取と抗リウマチ薬の治療効果に相関がみられた。この関連はスペイン人患者では認められなかったことから、魚の摂取が治療に与える影響は地域・人種によって異なる可能性が示唆された。n-3系PUFA摂取と抗リウマチ薬の効果との関連を詳細に検討するため、現在前向き観察研究を実施している。

研究成果の学術的意義や社会的意義

This study sheds light on the beneficial effect of consumption of fish rich in n-3 polyunsaturated fatty acids on treatment response in patients with rheumatoid arthritis, while highlighting the possible variability of this effect in different populations due to their different characteristics.

研究成果の概要（英文）：Dietary habits may influence the course of rheumatoid arthritis (RA), a chronic inflammatory disease that primarily affects the joints. This study aimed to investigate whether the consumption of fish rich in n-3 polyunsaturated fatty acids (PUFA) had an effect on treatment response in Japanese and Spanish patients with RA. In a retrospective observational study, a correlation was found between the consumption of n-3 PUFA rich fish at least once a week and the therapeutic response to antirheumatic drugs in Japanese patients. This association was not observed in Spanish patients, suggesting that the impact of fish intake on treatment may vary by region and race. A prospective observational study is currently underway to examine in detail the association between intake of fish rich in n-3 PUFA and the efficacy of antirheumatic drugs.

研究分野：59040

キーワード：Rheumatoid arthritis Diet Targeted therapy Fish consumption n-3 PUFAs

科研費による研究は、研究者の自覚と責任において実施するものです。そのため、研究の実施や研究成果の公表等については、国の要請等に基づくものではなく、その研究成果に関する見解や責任は、研究者個人に帰属します。

1 . 研究開始当初の背景

Rheumatoid arthritis (RA) is a systemic autoimmune disorder that primarily affects the joints causing joint swelling, pain, bone destruction and systemic features. The pathogenesis of RA is unknown, but genetic, hormonal, immunological and environmental factors combine to contribute to the development of the disease.

In recent years, the advent of molecular targeted therapies including biologics agents and Janus kinase (JAK) inhibitors that target specific components of the immune response have contributed to dramatic progress in the treatment of RA. With these therapeutic advancements, many patients with RA have experienced favourable outcomes (responders); however, disease control remains challenging for some patients (non-responders).

Diet and nutrition are considered environmental factors that can affect both the course of RA and the response to pharmacotherapy. Clinical trials have shown that the Mediterranean diet or supplementation with fish oil rich in n-3 polyunsaturated fatty acids (PUFA) have positive effects in the clinical course of RA [1]. It was also reported that RA patients who eat fish more than twice a week had significantly lower disease activity than patients who consumed fish never or less frequently [2]. Notably, both Japanese diets and Mediterranean diets are known for their high fish consumption. Hence, these two populations serve as valuable cohorts for investigating the impact of diet on RA.

2 . 研究の目的

The study aimed to investigate the relationship between consumption of fish rich in n-3 PUFA and treatment responses in patients with RA receiving targeted therapies in two distinct cohorts, one from Japan and the other from Spain. The study consisted in an initial Retrospective phase followed by Prospective phase.

3 . 研究の方法

Retrospective Study Phase

We conducted a collaborative international cross-sectional retrospective study involving patients with RA receiving targeted therapies, including biologics or JAK inhibitors, attending either Hokkaido University Hospital in Sapporo (Japan) or Hospital Virgen de las Nieves in Granada (Spain) (Fig 1).

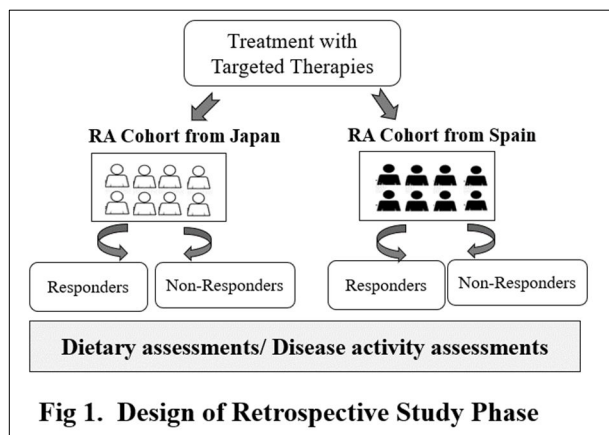


Fig 1. Design of Retrospective Study Phase

After obtaining the approval of the ethical review board of the two institutions and the patients' written informed consent, each patient was provided with two self-administered dietary questionnaires. The brief-type self-administered diet history questionnaire (BDHQ) [3] and a detailed fish frequency questionnaire (DFFQ) to document the food consumption over the last month.

At the study entry, disease activity was comprehensively evaluated by qualified rheumatologists., encompassing the disease activity score 28 (DAS28) erythrocyte sedimentation rate (ESR), DAS28 C-reactive protein (CRP), 28-tender joint count, 28-swollen joint count, ESR, CRP, and the patient's global assessment of disease-related general health using a visual analogue scale. The patients who responded to molecular targeted therapy (responder group) were defined as cases with DAS28-ESR < 2.6 and DAS28-CRP < 2.4, and the control group was the non-responders. Medical history, clinical characteristics, laboratory results and medication records were collected through a retrospective review of the patients' electronic medical records.

The association of patients' characteristics, the amount, and frequency of fish intake in the Responder and non-Responder group were evaluated using Chi-squared test, Fisher's exact test, and contributing factors to the Responder group were assessed using multivariate logistic regression analysis.

Prospective Study Phase

After completing the retrospective study phase, we conducted a prospective observational non-intervention study with a duration of 12 weeks in the Japanese RA cohort. The study involved adult RA patients initiating a new targeted therapy who attended Hokkaido University Hospital in Sapporo (Japan) (Fig 2). The prospective study protocol was approved by the ethical review board of Hokkaido University Hospital.

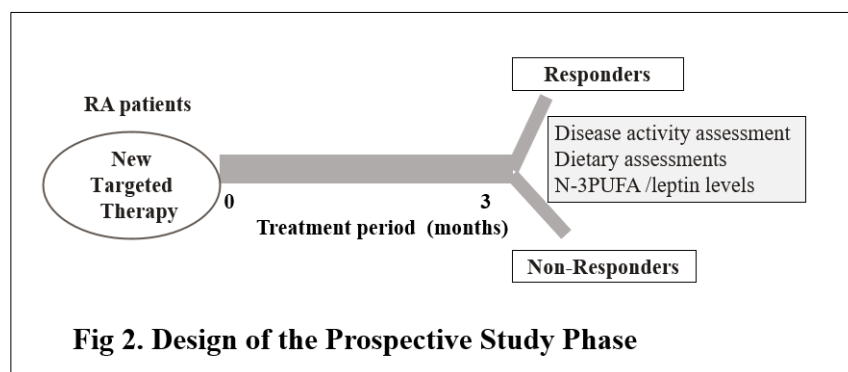


Fig 2. Design of the Prospective Study Phase

At the study entry (Visit 1), after signing a written informed consent, eligible patients were given two self-administered food frequency questionnaires, the BDHQ) and the DFFQ to document the food consumption over the last month. Patients were assessed for disease activity by qualified rheumatologists including DAS28-ESR, DAS28-CRP, 28-tender joint count, 28-swollen joint count, ESR, CRP, the patient's global assessment of disease-related general, the physician's global assessment of disease-related general health and the patient's pain assessment using visual analogue scales.

At Visit 2, which took place after three months of the initiation of the new treatment, patients completed two dietary assessments and were assessed for disease activity as described in Visit 1. Patients were defined as responders or non-responders to the new targeted therapy according to European League Against Rheumatism response criteria for clinical trials [4,5]. A serum sample was collected at this visit for laboratory determination of serum levels of PUFA and leptin.

The target number of patients for the prospective phase of the study was calculated based on results from the retrospective study. Taking into account the 10% dropout rate, we set the target number of patients at 60 patients.

4 . 研究成果

Retrospective Study Phase

In the Japanese cohort, 218 patients with RA were recruited of which 205 were eligible after excluding cases with insufficient data on disease activity assessment, insufficient responses on the dietary questionnaires or for other reasons.

Among the 205 included patients, 162 were female, with a median age of 67 years. Eighty-seven % of patients were treated with biologics and 13% with JAK inhibitors. Almost all the patients (99%) reported consuming fish at least one a week. The responder group criteria were met in 59% of the patients.

The estimated daily intake of n-3 PUFA was higher in the responder group compared to the non-responder group ($p = 0.04$). Moreover, a higher frequency of intake of fish rich in n-3 PUFA was observed in the responder group compared to the non-responder group (30% vs.14%, $p = 0.01$). Multivariate logistic regression analysis indicated that consuming n-3 PUFA rich fish at least once a week was an independent factor contributing to favourable outcomes in the responder group.

In the Spanish Cohort, 117 patients with RA were recruited of which 74 were eligible after excluding cases with insufficient data on disease activity assessment, insufficient responses on the dietary questionnaires or for other reasons.

Among the 74 included patients, 58 were female, with a median age of 60 years. 96% were on treatment with biologics, and 4% with JAK inhibitors. All the patients in this cohort reported consuming fish at least one a week. A total of 36% of patients met the responder group criteria.

No significant differences were found between the responder and non-responder groups in the estimated daily intake of n-3 PUFA ($p=0.11$) or in the frequency of consumption of fish rich in n-3 PUFA in this cohort (26% vs. 25%, $p = 1.00$).

The manuscript, which includes comprehensive data from the analysis of the characteristics and outcomes of the two retrospective study cohorts, is now complete and ready for submission to a scientific journal. We are currently awaiting written approval from several contributors. As the manuscript has not yet been published in a scientific journal, I unfortunately cannot provide every detail of the results in this report. However, I can assure you that we are committed to quickly start the submission process once the necessary approvals have been obtained.

Prospective Study Phase

The prospective phase of the study began after the completion of the retrospective phase, using the results of the retrospective analysis to establish the target population.

At the time of writing this report, we have enrolled fifty RA patients who have started a new targeted therapy, and all of them have completed their initial visit. Six patients were subsequently excluded, mainly due to medication withdrawal or failure to attend the second visit.

Thirty-two patients have completed the second visit after three months of treatment with the evaluation of treatment response, dietary assessments, and sample collection for analysis. Despite not yet reaching our target enrollment of 60 patients, the study continues until this milestone is achieved and all patients complete their second visit.

Due to the prospective design of the study, a preliminary analysis of the results is currently not possible. Instead, the analysis will be carried out after completion of the data collection of the two visits of all patients. The results obtained will be shared with the scientific community and society through publication in a scientific journal and presentation at conferences.

Conclusion

This study shows that consumption of fish rich in n-3 PUFA may benefit treatment response in Japanese RA patients undergoing molecular targeted therapies. However, this association was not observed in the Spanish population suggesting that the impact of fish consumption on treatment outcomes may vary between populations and may be attributable to several factors, including the diverse characteristics of the populations. A prospective observational study is currently underway to examine in detail the benefits of n3-PFA intake on the response to targeted therapies in Japanese RA patients.

References

1. Petersson S, Philippou E, Rodomar C, et al. The Mediterranean diet, fish oil supplements and Rheumatoid arthritis outcomes: evidence from clinical trials. *Autoimmun Rev* 2018;17:1105-14.
2. Tedeschi SK, Bathon JM, Giles JT, et al. Relationship Between Fish Consumption and Disease Activity in Rheumatoid Arthritis. *Arthritis Care Res (Hoboken)* 2018;70:327-32.
3. Kobayashi S, Murakami K, Sasaki S, et al. Comparison of relative validity of food group intakes estimated by comprehensive and brief-type self-administered diet history questionnaires against 16 d dietary records in Japanese adults. *Public Health Nutr* 2011;14:1200-11.
4. Aletaha D, Neogi T, Silman AJ, et al. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;62:2569-81.
5. Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;73:492-509.

5 . 主な発表論文等

〔雑誌論文〕 計0件

〔学会発表〕 計15件（うち招待講演 3件 / うち国際学会 6件）

1 . 発表者名 Tarumi M, Amengual O, Navidad Fuentes M, Yasuda M, Kosumi Y, Takeyama S, Yoshimura M, Ninagawa K, Aso K, Hisada R, Kono M, Fujieda Y, Kato M, Caliz R, Atsumi T
2 . 発表標題 Effect of fish intake on patients with rheumatoid arthritis using biologics or janus kinase inhibitors: a joint research in Japan and Spain
3 . 学会等名 The Annual European Congress of Rheumatology (EULAR). Vienna, Austria, 12-15 June 2024 (国際学会)
4 . 発表年 2024年

1 . 発表者名 Tarumi M, Amengual O, Yasuda M, Kosumi Y, Takeyama S, Hisada R, Kono M, Fujieda Y, Kato M, Atsumi T
2 . 発表標題 Fish consumption influences treatment response in patients with rheumatoid arthritis on molecular targeted therapy
3 . 学会等名 第68回日本リウマチ学会総会・学術集会. International Concurrent Workshop. 2024年4月18~ 20日, 神戸
4 . 発表年 2024年

1 . 発表者名 Amengual O
2 . 発表標題 The influence of dietary fish consumption in the treatment of rheumatoid arthritis
3 . 学会等名 Fourth meeting of the Association of Spanish Researchers in Japan. Tokyo, Japan, 4-5 November 2023
4 . 発表年 2023年

1 . 発表者名 Tarumi M, Amengual O, Navidad Fuentes M, Yasuda M, Kosumi Y, Takeyama S, Yoshimura M, Ninagawa K, Aso K, Hisada R, Kono M, Fujieda Y, Kato M, Caliz R, Atsumi T
2 . 発表標題 Relationship between fish consumption and response to treatment with molecular targeted therapies in patients with rheumatoid arthritis
3 . 学会等名 The Annual European Congress of Rheumatology (EULAR). Milan, Italy, 31 May-3 June (国際学会)
4 . 発表年 2023年

1. 発表者名 Tarumi M, Amengual O, Fujieda Y, Navidad Fuentes M, Tsuchida N, Yasuda M, Nishino K, Kosumi Y, Takeyama S, Yoshimura M, Ninagawa K, Aso K, Kono M, Kato M, Caliz Caliz R, Atsumi T.
2. 発表標題 Intake of fish rich in n-3 polyunsaturated fatty acids is associated with good response to treatment in rheumatoid arthritis patients receiving targeted therapies
3. 学会等名 The Annual European Congress of Rheumatology (EULAR). Copenhagen, Denmark, 1-4 June 2022 (国際学会)
4. 発表年 2022年

1. 発表者名 Amengual O
2. 発表標題 Study of the effect of fish consumption on treatment response in rheumatoid arthritis.
3. 学会等名 Third meeting of the Association of Spanish Researchers in Japan (ACE-Japon). Tokyo, Japan 4-5 November 2022
4. 発表年 2022年

1. 発表者名 Amengual O, Tarumi M, Fujieda Y, Hisada R, Kono M, Kato M, Atsumi T.
2. 発表標題 Effect of consumption of fish rich in n-3 polyunsaturated fatty acids on treatment response in patients with rheumatoid arthritis
3. 学会等名 22nd International Union of Nutritional Sciences International Congress of Nutrition (IUNS-ICN), Tokyo, Japan 6-11 Dec 2022 (国際学会)
4. 発表年 2022年

1. 発表者名 Sakiyama K, Abe N, Fujieda Y, Tada M, Tsuchida N, Nishino K, Moriya H, Yasuda M, Kono M, Kato M, Amengual O, Atsumi T
2. 発表標題 Dynamic functional connectivity associated with response to biologics in rheumatoid arthritis and spondyloarthritis
3. 学会等名 第66回日本リウマチ学会総会・学術集会、2022年4月25日～4月27日、横浜
4. 発表年 2022年

1. 発表者名 垂水 政人, Olga Amengual, 安田 充孝, 小住 由衣, 竹山脩平, 吉村 大, 久田 諒, 河野 通仁, 藤枝 雄一郎, 加藤 将, 渥美 達也
2. 発表標題 関節リウマチ患者の魚の摂取量と分子標的治療の治療経過との関連
3. 学会等名 第37回日本臨床リウマチ学会、2022年10月29日、札幌
4. 発表年 2022年

1. 発表者名 Olga Amengual
2. 発表標題 Advances in the Management of Rheumatoid Arthritis
3. 学会等名 School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan, 20 June 2022 (招待講演)
4. 発表年 2022年

1. 発表者名 Olga Amengual
2. 発表標題 Advances in the treatment of Rheumatoid Arthritis
3. 学会等名 Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan, 12 July 2021 (招待講演)
4. 発表年 2021年

1. 発表者名 Olga Amengual
2. 発表標題 Rheumatology and the Spectrum of rheumatic diseases
3. 学会等名 Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan, 20 January 2021 (招待講演)
4. 発表年 2021年

1. 発表者名 Sugawara M, Fujieda Y, Noguchi A, Tanimura S, Shimizu Y, Nagakawa I, Takahashi H, Kono M, Kato M, Oku K, Amengual O, Atsumi T
2. 発表標題 Prediction of responder and non-responder to JAK inhibitors in patients with rheumatoid arthritis: A pilot study with integrative cluster analysis
3. 学会等名 The American College of Rheumatology Convergence 2020 Annual Meeting, virtual congress, 5-9, Nov (国際学会)
4. 発表年 2020年

1. 発表者名 Yoshimura M, Fujieda Y, Kono Michihito, Kato M, Oku K, Amengual O, Atsumi T
2. 発表標題 The association between the risk of venous thromboembolism and disease activity in patients with rheumatoid arthritis: A retrospective observational study
3. 学会等名 The American College of Rheumatology Convergence 2020 Annual Meeting, virtual congress, 5-9, Nov (国際学会)
4. 発表年 2020年

1. 発表者名 Yoshimura M, Fujieda Y, Kono M, Kato M, Oku O, Amengual O, Atsumi T
2. 発表標題 The risk assessment of developing deep venous thrombosis in patients with rheumatoid arthritis
3. 学会等名 第64回日本リウマチ学会総会・学術集会、2020年8月17日-9月15日
4. 発表年 2020年

〔図書〕 計0件

〔産業財産権〕

〔その他〕

-

6. 研究組織

	氏名 (ローマ字氏名) (研究者番号)	所属研究機関・部局・職 (機関番号)	備考
研究分担者	渥美 達也 (Tatsuya Atsumi Tatsuya Atsumi) (20301905)	北海道大学・医学研究院・教授 (10101)	

7. 科研費を使用して開催した国際研究集会

〔国際研究集会〕 計0件

8 . 本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関
---------	---------