Conclusion: Our present study suggests that tofacitinib is effective in real-world settings even without concomitant MTX. Our results also suggest that for continuous use of tofacitinib without lack of efficacy, use tofacitinib earlier during switching strategy for RA patients who have failed to be treated with bDMARDs is better.

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AB0345 EFFICACY OF JAK INHIBITORS IN REFRACTORY RHEUMATOID ARTHRITIS

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Background: Disease-modifying antirheumatic drugs (DMARDs) have been the main agents for treating rheumatoid arthritis (RA) unless there are serious clinical restrictions or contraindications such as comorbidities. With inefficacy of conventional synthetic DMARDs (e.g., methotrexate), biological DMARDs (bDMARDs) are now available to suppress progression of joint destruction. However, bDMARDs cannot control disease activity in some patients, so JAK inhibitors targeting different cytokines are expected to be beneficial.

Objectives: This study investigated factors associated with the efficacy and continuation of JAK inhibitor therapy in patients with refractory RA for whom disease activity was not adequately controlled even with multiple sequentially administered bDMARDs with different targets.

Methods: We obtained the number of bDMARDs used and the various reasons for discontinuing therapy in our hospital from January 2005 to December 2019. Kaplan-Meier analysis was used to obtain the therapy continuation rate, and the log-rank test was used to examine the difference in therapy continuation rate. Refractory RA was defined as RA with inefficacy with 3 or more bDMARDs with different targets (1 or more tumor necrosis factor inhibitor, a selective costimulation modulator abatacept, and an interleukin 6 receptor inhibitor tocilizumab). We then examined patients with refractory RA who had received tofacitinib (TOF) or baricitinib (BAR) therapy after discontinuation of a series of bDMARDs due to unsatisfactory response. Various statistical tests were performed to identify predictors of ≥ 6 -month continuation of JAK inhibitor therapy that achieves low disease activity without increases in prednisolone (PSL) use. Explanatory variables included characteristics of patients at initiation of TOF or BAR therapy: age, sex, disease duration, number of bDMARDs previously used, concomitant methotrexate dose, concomitant PSL dose, DAS28-ESR value, presence of rheumatoid factor or anti-CCP antibodies, and MMP-3 level.

Results: A cumulative number of 782 bDMARDs were administered to 362 RA patients by December 2019. The most common reason for discontinuation was inefficacy (51.8%), followed by adverse events including deaths (30.1%), patients' circumstances such as hospital transfer (9.2%), switch to biosimilars (5.2%), and remission (3.7%). The bDMARDs continuation rate and the number of bDMARDs used were 69.6% and 2.17 for 5 years and 53% and 2.83 for 10 years, respectively, if the switch was considered to be continuous due to insufficient effect. The 6-month continuation rates were not significantly different between TOF and BAR (60 patients [62.3%] vs. 39 patients [81.3%], respectively; $P = 0.147$). In patients with refractory RA, continuation rates were not significantly different between TOF and BAR (19 patients [42.1%] vs. 11 patients [54.5%], respectively; $P = 0.86$). Only TOF-treated patients, not BAR-treated patients, showed significant differences in disease duration (226.1 months in the continued group vs. 111.8 months in the discontinued group; $P = 0.035$) and concomitant PSL dose (0.71 mg vs. 4.0 mg, respectively, $P = 0.045$).

Conclusion: There are not a few patients with refractory rheumatoid arthritis. These findings, albeit retrospective, suggest that low concomitant PSL dose and long disease duration at the time of TOF therapy initiation were factors for TOF continuation. Therapy continuation rate was decreased in patients with refractory RA, and further study on switching therapy between different JAK inhibitors is anticipated.

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AB0346

THE NUMERAL CHANGES OF PERIPHERAL LYMPHOCYTE SUBSETS IN PATIENTS WITH RHEUMATOID ARTHRITIS AND THEIR RESTORATIONS AFTER RECEIVED COMBINED IMMUNOMODULATORY THERAPY

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Background: Rheumatoid arthritis (RA) is an aggressive immune-mediated joint disease with synovial inflammation and joint destruction characterized by abnormal immune responses to self-antigens¹. An imbalance in pro- and anti-inflammatory lymphocyte subsets has been considered to contribute to the pathogenesis of RA². However, the detailed lymphocyte statuses of RA patients are required clarified and the effect of immunomodulatory therapy on the lymphocyte subsets is unclear³.

Objectives: To investigate the status of lymphocyte subsets in peripheral blood (PB) of RA patients at relatively large-sample size and the changes of them after our immune regulatory combination treatment.

Methods: This cross-sectional study enrolled 3016 patients with RA who met the ACR's revised RA diagnostic classification in 1987 as well as 206 healthy controls (HCs). Among these participations, 1415 patients have received the treatment of immunomodulatory drugs (IMiDs) such as low-dose interleukin-2, rapamycin, metformin, retinoic acid etc. Flow cytometry (FCM) was used to measure the levels of PB lymphocyte subgroups and CD4⁺T subsets in RA patients before and after the treatments and HCs. Data were expressed as mean $\pm$ standard deviation to the distribution. Independent-samples T test and paired-samples T test were applied. P value < 0.05 were considered statistically significant.

Results: Compared with HCs, patients with RA had a lower absolute numbers of total T, CD8⁺T, NK and Tregs ($P < 0.05$), decreased percentages of NK, Th1, Th2 and Th17 ($P < 0.05$), but higher ratios of Tregs/Tregs such as Th1/Tregs and Th17/Tregs ($P < 0.05$), indicating a disturbance of immune systems (Figure 1). After receiving combined immunomodulatory therapy, the absolute numbers of T, B, CD4⁺T, CD8⁺T, NK, Th1, Th17 and Tregs were dramatically increased ($P < 0.05$) and the percentages of B, Th1, CD4⁺T and Tregs were also increased ($P < 0.05$). Although these subsets increased globally, the ratio of Tregs/Tregs such as Th2/Tregs and Th17/Tregs tended to decrease, suggesting a rebalance of immune systems (Figure 2).

Conclusion: Impaired peripheral lymphocytes especially insufficiency of Tregs might played an important role in pathogenesis of RA. Immunoregulatory combination therapies could promote the proliferation and functional recovery of Tregs in patients and help to alleviate disease activity.

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Figure 1: Comparison of lymphocyte subsets in peripheral blood between HCs (n=206) and RA patients (n=3016). All the lymphocyte subsets were analyzed by detected by flow cytometry combined with standard absolute counting beads. Data were presented as mean $\pm$ SD and statistical analysis was determined by two-tailed unpaired t-test. Patients had lower levels of T, CD8⁺T, NK and Tregs (A and B), decreased percentages of NK, Th1, Th2 and Th17 (C and D), and higher ratios of Tregs/Tregs such as Th1/Tregs and Th17/Tregs in RA compared with those of HCs (E). HC: healthy control * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Figure 2: Changes of peripheral lymphocyte subsets after immune new regulatory combination therapies (n=1415). Data were presented as mean±SD and statistical analysis was determined by two-tailed paired t-test. Absolute number of T, B, CD4+T, CD8+T, NK, Th1, Th17 and Tregs were significantly increased (A and B). The proportion of B, Th1, CD4+T and Tregs were also increased (C and D), while the ratio of Tregs/Tregs such as Th2/Tregs and Th17/Tregs had a tendency to decrease after immune new regulatory combination therapies (E). *P<0.05, **P<0.01, ***P<0.001.

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AB0347 INCREASING TO OPTIMAL METHOTREXATE DOSE MIGHT BE A BETTER TRADITIONAL DMARD STRATEGY IN RA TREATMENTS: A RANDOMIZED CASE-CONTROL TRIAL OF HAKKA PEOPLE IN SOUTHERN CHINA

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Background: The optimal methotrexate (MTX) dose is defined as 0.3mg/kg/week or ≥ 20 mg/week at 6 months. [1] Considering average weight of Chinese, [2] the optimal MTX should be >15 mg/w. However, not more than 30% in 25191 RA cases ever had MTX treatment in CREDIT (Chinese Registry of Rheumatoid arthritis). [3] The biggest concern is side effects of MTX. Our study is to investigate whether increasing MTX would get better results accompanied with more side effects to Chinese people.

Objectives: Hakka people have the purest genes of the majority people-Han in China. It is planned to recruit 160 RA patients in Meizhou, where is a gathering place of Hakka people.

Methods: The RA volunteers had no relief with 10mg/w oral dose of MTX with/without other 1-2 inadequate dose of DMARDs for at least 3 months. They were randomly divided into 1:1 groups. The experimental group would be treated with original DMARDs and incremental MTX (gradually increased to the optimal oral dose (0.3mg/kg/w) in the first 12 weeks and folic acid (the dose adjusted on demand with range from 5mg/w to 5mg tid). While the control group would be treated with original MTX dose(10mg/w) but incremental original DMARDs(gradually increased to the maximum dose in the first 12 weeks). The two groups would keep the treatment at 12th week last to the 36th week, and the efficacy and safety indexes would be evaluated during the whole study.

Results: 1)We planned to recruit 160 RA patients in our study. 46 Hakka RA patients were enrolled in the study so far. 2 of 46 finished the 24th week visit and 24 finished the 36th week visit. The average age is 54.2 ± 9.3 years old, the average weight is 59.1 ± 11.1 kg, and the female to male ratio is 41:5.

2)The average Folic acid dose is 14.4 ± 9.5 mg/w in the experimental group at the 12th week.

3)The morning stiffness time, PGA, PhGA, HAQ, DAS28 were better in experimental group after 12 weeks though slightly worse during 0-12 weeks. 100%(12) patients in experimental group, while 66.67%(8/12) in control group reach ACR20.

4) Only 1 case(5.9%,1/23)had adverse event while 6 cases (26%,6/23) occurred adverse events. All events were mild level. 1 case (4.2%,1/23) in control group withdrew from the study because the disease was getting worse during 0-24 weeks.

Conclusion: Hakka patients in China might have better outcomes due to increasing MTX to the 0.3mg/kg/w dose than increasing the other DMARDs. Therefore, We recommended the Chinese patients choose MTX as first incremental DMARD. The appropriate dose of Folic acid plus with the optimal dose of MTX in our study is higher than previous studies (such as 13.0 ± 4.8 mg/w reported by Gaujoux-Viala, 2018[1]). We recommended Chinese patients take 15mg/w folic acid to prevent MTX side effects in view of lower folic acid level in Chinese population.[3]

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AB0348 THE EFFECTIVENESS AND SAFETY OF BARICITINIB AFTER INSUFFICIENT RESPONSE TO bDMARDs OR tsDMARDs IN PATIENTS WITH RA FROM JAPANESE MULTI-CENTER REGISTRY: 24-WEEK OUTCOMES

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Background: EULAR has issued updated guidelines for the management of rheumatoid arthritis (RA) using conventional, biologic, and targeted synthetic DMARDs. In the 2019 update, the task force revised the preference of bDMARDs over tsDMARDs. In routine clinical practice, baricitinib is commonly used as second line or after. However, there is little information about the clinical efficacy and safety profile of baricitinib after failure of the previous agent, including another tsDMARD.

Objectives: The aim of this study was to evaluate the short-term effectiveness and safety profiles of baricitinib after insufficient response (IR) to bDMARDs or tsDMARDs in patients with RA in clinical settings.

Methods: RA patients who had been treated with baricitinib after failure of the previous agent were registered in the TBCR, a Japanese multicenter registry for RA patients treated with biologics or JAK inhibitors and followed for at least 24 weeks. Patients were divided into two groups according to the cause of failure of the previous treatment; IR ("After IR" group) and the others ("After non-IR" group). "After IR" group was further divided into four groups according to the previous agent; TNF inhibitor (TNFi group), IL-6 receptor inhibitor (IL-6Ri group), abatacept (ABT group) and tofacitinib (Tofa group). We assessed disease activities by CDAI score and drug retention rates between these groups. Furthermore, discontinuation rates due to IRs and adverse events (AEs) were evaluated.

Results: A total of 86 consecutive RA patients were registered in this study. The previous treatment was as follows; TNF inhibitor: 38 (44.2%), IL-6 receptor inhibitor: 23 (26.7%), abatacept: 11 (12.8%), tofacitinib: 13 (15.1%) and the other: 1 (1.2%). The cause of failure of the previous therapy were IRs (n=74: 86%), AEs(n=6: 7.0%) and the others (n=6: 7.0%). In "After IR" group, the most common

previous agents were TNFis (Table 1). While the percent change in CDAI was decreased at week 12 in all groups, those in Tofa group showed lower rates of improvement in CDAI compared to the others at week 24 (Figure 1). Drug retention rate at 24-week was 59.4% in TNFi group, 90.5% in IL-6Ri group, 54.5% in ABT group and 77.8% in Tofa group (Figure 2). In the present study cohort, seven patients developed herpes zoster. All seven patients were treated with antiviral agents for herpes zoster and restarted baricitinib treatment (these cases were not treated as discontinuation due to AEs in this study). The overall Cumulative discontinuation rate due to IRs and AEs at 24 weeks were 9.7% and 7.3%, respectively.