Very low dose, add-on prednisolone in patients with newly diagnosed rheumatoid arthritis: a randomised placebo-controlled study

Research in context:

(i) What is the existing evidence before this study based on an up-to-date literature search? State clearly whether research on a similar topic has been/is being carried out. Outline the research approaches in other studies and highlight their deficiencies and the research gap.

There are conflicting views from international guidelines on the use of glucocorticoids (GC) as bridging therapy in patients with newly diagnosed rheumatoid arthritis (RA). While GC, typically at a dose of prednisolone ≥5mg daily, is definitely effective in controlling RA disease activity, it is associated with dose-dependent toxicities. There are emerging evidence supporting prednisolone dose <5mg daily is not associated with significant infection risk or bone loss. Recent real-world registry data also suggest very low dose GC are cardiovascular safe in short and long term. Two GC tapering studies provided indirect evidence that very low dose GC could help RA disease control. However, the therapeutic effect of very low dose GC (prednisolone dose <5mg daily) as bridging therapy has not been formally investigated. Therefore, we plan to conduct the first randomised placebo-controlled trial evaluating the efficacy and safety of very low dose add-on GC in patients with newly diagnosed RA.

(ii) How will this study add value to existing evidence to improve patient care, population health,
influence clinical practice and/or health services management, or inform health policy in Hong Kong and elsewhere?

The results of our study will provide immediate evidence supporting the use of very low dose GC as bridging therapy while initiating conventional synthetic disease modifying anti-rheumatic drugs, which remain the first-line treatment for all patients with newly diagnosed RA. The proposed low dose prednisolone prescription can be directly applied to daily clinical care. The aim is to offer rapid symptomatic relief, abolish inflammation promptly and treat RA to the target of disease remission. This coincides with the contemporary treatment strategies of RA which have been well proven to be pivotal for improving patient long-term outcomes. Disability of RA patients will be minimized. Their quality of life and productivity can be restored as early as possible. Expensive advanced therapies with variable access in different health-care settings can be reserved for refractory cases. The treatment algorithm of the study can be adopted by future RA management recommendations. The ultimate goal will be to improve patient health and reduce the overall socio-economic burden of the disease.

b(ii). **Introduction:**
Rheumatoid arthritis (RA) is a common chronic inflammatory arthritis affecting 0.35% of the population in Hong Kong (1). Uncontrolled arthritis can lead to pain, disability and decreased quality of life. We also found that the disease carried substantial socioeconomic costs (2). The contemporary management strategies have considerably improved the long-term outcomes of RA but come with toxicity and cost issues. Local and international treatment recommendations are largely similar, involving early initiation of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and prompt up-titration of medications if tight disease control

cannot be achieved (3-6). The major discrepancy between guidelines concerns the use of glucocorticoids (GCs) before csDMARDs become fully effective – as a bridging therapy.

GCs were introduced in the 1950s, and have been widely available in all health-care settings. Despite its safety concerns, GC stands as a potent anti-inflammatory drug useful for prompt and reliable relief of RA symptoms. While it is agreed that long-term usage is harmful, GC is still commonly prescribed especially at the initial presentation of active disease while awaiting the effect of csDMARDs (7). In our recent retrospective study using real-world local territory-wide data, 37.7% of patients with early RA (mean disease duration 0.7 year) were on GC (8). Intriguingly, the latest RA management recommendations from the American College of Rheumatology (ACR, updated in 2021) and European Alliance of Associations for Rheumatology (EULAR, updated in 2022) are divergent in terms of GC bridging therapy (5, 6). ACR conditionally recommended the initiation of csDMARD without short-term GC (over with GC) for patients with active disease, meanwhile acknowledging that shortterm GC is often needed for symptom alleviation. It also strongly recommended against using GC for longer than 3 months. On the contrary, EULAR recommended that short-term (not more than 3 months) GC should be considered when initiating csDMARD but should also be tapered and discontinued as quickly as clinically feasible, given the robust evidence of efficacy of a combination of csDMARD with GC (9). Similarly, while the Hong Kong Society of Rheumatology ecommended that bridging GC might be considered when starting csDMARDs, the latest update of the Asia Pacific League of Associations of Rheumatology RA treatment recommendation did not mention the usage of GC in addition to csDMARD monotherapy (3, 4). Despite the distinctly different recommendation statements, all authorities clearly acknowledged the therapeutic effect as well as toxicity of GC, and emphasized minimization of the dose and duration of use.

Among the extensive list of side effects, increased cardiovascular disease (CVD) risks associated
with GC use is of particular concern. CVD is the most common comorbidity and the leading cause of mortality in patients with RA (10). The excess CVD risk in RA is mediated by the underlying chronic systemic inflammation, increased prevalence of traditional cardiovascular risk factors, and the use of various pharmacotherapeutic agents including GC and arguably JAK inhibitors (11). GC increases the risk of CVD by adversely affecting blood pressure, sugar metabolism and lipid profile. On the other hand, knowing the key inflammatory cytokines in RA, for example, TNF-alpha and IL-6 also promote atherosclerosis, GC may be able to exert some cardiovascular protective effect via suppression of these cytokines at transcription level (12-14). In addition, nuclear factor-kappa B (NF-κB) has been revealed to be a pivotal upstream source for these pro-inflammatory signals involved in the pathogenesis of both RA and atherosclerosis, and GC is a known potent inhibitor of NF-κB expression (15-17). Given the toxicities associated with GC are dose-dependent, finding a safe threshold dose and duration of GC use in RA is of great clinical interest.

A previous observational study of 779 patients with RA showed that the risk of all-cause and CVD mortality increased progressively when the daily dose of prednisolone was above 7.5 mg (18). We have recently performed a population-based retrospective cohort study using real-world data and recruited 12,233 RA patients with 105,826 patient-years of follow-up (19). The salient findings of our study are that prednisolone <5 mg daily was not associated with major adverse cardiovascular events (MACE) after adjusting for time-varying conventional risk factors, inflammatory markers and other medications, while prednisolone ≥5 mg daily doubled

the risk of future incident MACE, when compared with no GC use. Our findings are in line with the another recent large study using the CorEvitas registry in the United State, which reported a dose-dependent increased short-term (up to 12 months) risk of CVD events with prednisolone ≥5 mg daily, while the dose <5 mg daily was found to be CVD safe (20). In the Glucocorticoid LOw-dose in RheumatoId Arthritis (GLORIA) trial, patients with RA aged above 65 on standard of care with DAS28≥2.6 were randomized to receiving add-on prednisolone 5 mg daily for 2 years vs placebo (21). Among 224 patients receiving add-on prednisolone, 10 (4.5%) developed MACE; while 6 (2.7%) out of 225 patients in the placebo arm developed events. There was no statistically significant difference between the two groups. However, the follow-up duration of 2 years might not be adequate to reveal the long-term detrimental effects of GC. As prednisolone dose below 5 mg daily appeared to be cardiovascular risk neutral, it would be important to know whether this very low dose is in fact clinically effective in RA.

In the GLORIA trial mentioned above, add-on prednisolone 5 mg daily led to significantly lower RA disease activity and less radiographic progression, compared with placebo (21). The Circadian Administration of Prednisone in Rheumatoid Arthritis (CAPRA-2) study, another randomized controlled trial, also showed that add-on modified-release prednisolone 5 mg daily resulted in doubling of treatment response (22). The Steroid EliMination In Rheumatoid Arthritis (SEMIRA) trial compared stable patients with RA on 'tocilizumab with prednisolone 5 mg/day' versus 'tocilizumab with prednisolone tapering 1 mg every 4 weeks to 0 mg' (23). Although it was concluded that continuing prednisolone 5 mg/day was better for disease control (relative risk 0.83; 95% CI 0·71 to 0·97) at the end of the study (24 weeks), the flare-free proportion at 8 weeks was 0.96 and 0.97 in the tapered prednisolone and continued prednisolone groups respectively. This provided indirect evidence that prednisolone at 3 or 4 mg daily could still be clinically effective. In a double-blind GC withdrawal trial, patients with RA originally on prednisolone 5 mg daily were randomized to gradual tapering with 1–4 mg prednisolone daily or placebo (i.e., direct discontinuation of GC) (24). It was found that patients in the tapering group were more likely to withdraw GC without flare, again indicating that very low dose GC could help RA disease control. However, the efficacy of prednisolone <5 mg daily in RA has not been formally evaluated in clinical trials.

We have conducted a pilot open-label study evaluating the efficacy of add-on prednisolone 4mg daily in patients with recently diagnosed RA [unpublished]. We recruited 7 consecutive patients not on any DMARDs with at least moderate disease activity from 11/23 to 1/24. Their baseline clinical characteristics are shown in table 1. Prednisolone 4mg daily was started together with methotrexate. The participants were reassessed in 4 weeks. Improvement in RA disease activity was noted in most of the patients post-treatment. The mean Disease Activity Score 28–C-Reactive Protein (DAS28-CRP) decreased from 5.1 ± 0.7 to 3.7 ± 1.6 (p=0.042). There was no significant adverse event reported. However, as there was no control group, the results were confounder by the therapeutic effect of methotrexate. It is of note that from our large local real-world RA database, about a quarter of the exposure to GC (in terms of person-year interval) was below prednisolone 5mg daily, indirectly reflecting the clinical effectiveness and possibly safety of very low dose GC (19).

Despite the advent of biologic and targeted synthetic DMARDs, there is a trend in the RA research field to revisit the effect and safety of low dose GC (25). Back in 2016, the EULAR task force re-evaluated the harm and safety of low dose GC use, and proposed that the risk of long-term prednisolone ≤5 mg daily was acceptably low (26). Evidence in favor of the safety

of low dose GC in terms of bone health has been emerging, where prednisolone ≤5 mg daily did not seem to be associated with reduced bone-mineral density in the recent Glucocorticoid-induced Osteoporosis in Patients With Chronic Inflammatory Rheumatic Diseases or Psoriasis (Rh-GIOP) study (27). The GLORIA trial also provide partial reassurance with regard to infection risk which is another most recognized adverse event of GC therapy. After 2 years of 5mg/day prednisolone, the proportion of patients (all aged ≥65) with at least one adverse event of special interest (serious or glucocorticoids-related) was increased by 24%, mostly due to non-severe infections. The result sets a benchmark for the upper limit of harm, and the risk in a less vulnerable population with lower dose and shorter duration of GC use is expected to be lower. All in all, "*does the concomitant use of GCs at very low doses increase therapeutic success without producing unacceptable side effects?"* is explicitly listed as one of the top research agenda in the latest EULAR RA management recommendations published in 2023 (6).

We believe the half-a-century long controversy regarding GC use in RA boils down to one final clinical question that whether very low dose GC is an effective and safe bridging therapy, as 1) chronic GC use is unanimously not advisable, 2) very low dose GC (prednisolone < 5mg/day) appears to have no or minimal toxicity concern (28), and 3) prednisolone 4mg daily shows promising therapeutic effect in our preliminary study. Very low dose GC could be the universal add-on treatment for all RA patients initiating csDMARDs with an optimal benefit-risk ratio. To formally address this important clinical question, we plan to perform the first randomized controlled trial assessing the efficacy and safety of prednisolone 4 mg/day added to standard of care in patients with newly diagnosed RA. The results of our study are anticipated to be immediately implemental and can guide daily clinical practice.

c. **Aims and Hypotheses to be Tested:**
The aim of this study is to evaluate the efficacy of prednisolone 4mg/day added to standard of care in newly diagnosed RA patients with active disease. We hypothesise add-on prednisolone 4mg/day is efficacious compared to placebo in newly diagnosed RA patients with active disease.

d. **Plan of Investigation:**
(i) Study design
This is an investigator-initiated, single-center, randomized, placebo-controlled, double-blind study. The intervention duration is 10 weeks. The follow-up period is 24 weeks. The recruitment period is 30 months. The total study duration will be 3 years.

(ii) Methods
Primary outcome
The primary outcome is the change of DAS28-CRP at 4 weeks comparing prednisolone group and placebo group.

Secondary outcomes
1) Changes of RA disease activity at week-8, week-12 and week 24 comparing the 2 groups.
2) Changes of RA disease activity at different time points within the 2 groups.
3) Disability at different time points comparing the 2 groups.
4) Proportion of patients with adverse events comparing the 2 groups.
5) Independent predictors of RA disease control in all participants.

Treatment and clinical evaluations

All the participants (n=112) will be randomized in a 1:1 ratio to prednisolone (n=56) or placebo (n=56) group. Randomization will be performed using a computer-generated randomization list provided by the research pharmacist, adopting a permuted blocks design with block sizes of 4. Allocation concealment will be ensured by the use of sequentially numbered, opaque, sealed envelopes. Treatment will be masked to patients and investigators. The participants will be instructed to take one study capsule (prednisolone or placebo) daily for 10 weeks. For the prednisolone group, the dose of the active drug will be 4mg once daily for 4 weeks then tapering at 1mg/week every 2-week till off at week 10. All participants will also be given csDMARDs and treated to a target of DAS28 low disease activity (<3.2) at Prince of Wales Hospital (PWH) throughout the study period according to a standard protocol modified to our study based on the EULAR recommendation and the Hong Kong guideline on the use of DMARDs. Disease activity and adverse events will be monitored at 4 weeks, 8 weeks, 12 weeks and 24 weeks. Patients will be advised to reach out to the rheumatologists earlier if the condition changes unexpectedly. Changes in the dosage or addition of nonsteroidal anti-inflammatory drugs are allowed. Switching to a new csDMARD is possible in case of toxicity or intolerance. The use of b/tsDMARDs or additional systemic GC will be prohibited throughout the study. All medication changes will be documented in detail. Participants who required rescue b/tsDMARDs or systemic GC will be withdrawn from the study. They will be treated according to the standard of care with regular assessment till the end of the study. All patients will be given calcium and vitamin D supplements throughout the study period.

The following clinical variables will be assessed at each visit: erythrocyte sedimentation rate (ESR), CRP, number of swollen joints (0–28), number of tender joints (0–28), visual analogue scale (VAS) for pain (0–100 mm=most pain), VAS for patient's global assessment (0–100 mm=worst score), VAS for physician's global assessment (0–100 mm=worst score), and DAS28 score. The presence of rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) antibody with their respective serum levels will be documented at baseline. The number of damaged joints will be assessed at baseline and the end of the study. Rheumatoid factor status and anti-cyclic citrullinated peptide antibodies status will be determined at baseline. Functional disability is assessed by the disability index of HAQ (0-3=most functional disability). ACR20/50/70 responses are defined as at least 20%, 50%, and 70% improvement in swollen joint and tender joint counts, and three of five other variables (i.e., ESR or CRP, HAQ score, pain score, and physicians' and patients' global assessments). All assessments and consultations will be done by rheumatologists (investigators) with more than 10 years experience.

Preparation of study medications

Both the active drug (prednisolone) and placebo will be repackaged into capsules with identical appearance according to the standard operating procedure of the Clinical Research Pharmacy, School of Pharmacy, The Chinese University of Hong Kong. On entering the trial, each participant will be given a filled and labeled bottle, coded with a unique study number, which will be used for all future supplies of study drugs for that patient. Study treatment will remain masked for the patients, investigators, and study personnel throughout the trial. Code breaking is allowed in special circumstances by informing the Clinical Research Pharmacy or at end of the study.

Toxicity monitoring
To monitor the possible side effect of prednisolone and other medications, complete blood count, liver function test and renal function test will be performed at screening, week 4, week 8 and week 12 and week 24. Body mass index, blood pressure, blood sugar and lipid profile will be checked at baseline, week 4, week 8, week 12 and week 24. Chest x-rays will be obtained at screening and when clinically indicated. Hepatitis status and electrocardiogram will be done at screening. The treating physicians will record all adverse events (AEs) and, if necessary, make treatment adjustments in accordance with the protocol. Serious AEs (SAEs) are defined as the occurrence of life-threatening condition or death, a significant or permanent disability, a malignancy, hospitalization or prolongation of hospitalization, a congenital abnormality, or a birth defect. AEs of special interest (AESI) will also be collected which include any AE leading to drug discontinuation, MACE (myocardial infarction, cerebrovascular or peripheral arterial vascular event), newly occurring hypertension/diabetes/infection/cataract/glaucoma and fragility fracture.

iii) Subjects (with justification on the sample size)
Consecutive RA patients attending the rheumatology clinics of PWH will be screened for eligibility. The inclusion criteria are: 1) ≥18 year-old, 2) fulfilment of the 2010 ACR/EULAR classification criteria of RA, 3) never use of any DMARDs for RA, 4) disease activity score 28-C-reactive protein (DAS28-CRP) >3.2, and 5) Chinese subjects only. The exclusion criteria are: 1) pregnancy or premenopausal women planning pregnancy, 2) functional status class IV (limited in ability to perform usual self-care, vocational, and avocational activities), 3) use of systemic GC in recent one month, and 4) contraindications to prednisolone. A total of 112 patients who meet the criteria will be included.

A sample size determination was conducted for the primary outcome measurement, the difference in the change of DAS28-CRP at 4 weeks comparing the 2 groups, using Power Analysis and Sample Size Software (PASS version 11). From the published results of the GLORIA trial, the short-term (3 months) improvement in DAS28 in the prednisolone group and placebo group was 1.36±1.14 (baseline 4.40±1.04) and 0.73±1.21 (baseline 4.46±0.99) respectively (21). In our pilot study mentioned above, the improvement in mean DAS28 was -1.4 ± 1.3 post-treatment. Therefore, more conservatively, we expect the difference of the change of DAS28-CRP at 4 weeks to be 0.6 comparing the prednisolone and placebo group. At least 49 patients will be required in each group to achieve a statistical power of 0.8 with a two-sided α of 0.05. With an estimated dropout rate of 15%, a total sample size of 112 would be required.

The study will be submitted to The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee and the Central Institutional Research Board of the Hospital Authority for approval. It will also be submitted to the clinicaltrials.gov for registration. Written informed consent will be obtained from all participants prior to any of the trial procedure. The study will be conducted according to the Declaration of Helsinki and ICH-GCP guidelines.

(iv) Data processing and analysis
Patients who discontinue treatment or violate treatment protocol will be excluded from the analysis (per-protocol analysis). Missing data are assumed missing at random and will be treated using a multiple imputation method. Descriptive statistics will be used to present the baseline demographic and clinical variables included frequencies, means with standard

deviations and median with interquartile range. T-test or Mann-Whitney U test and Chi-square test or fisher exact test will be used to evaluate the differences in clinical variables between the prednisolone and the placebo group at baseline, depending on the data distribution. The primary outcome measurement, the difference in the change of DAS28-CRP at 4 weeks comparing the 2 groups, will be analyzed by T-test. Clinical variables which are significantly different between the 2 groups in the univariate analyses and are biologically plausible (eg. age, sex, disease duration, disease activity or treatment) will be adjusted in the multivariate logistic regression model to confirm the prednisolone treatment effect. The secondary outcomes on disease activity at week 8, week 12 and week 24 or disability in terms of HAQ at different time points will be compared likewise. The within group changes of these measurements before and after treatment will be examined using paired t-test or Wilcoxon signed-rank test. To look for the changes across study period across 2 groups, the repeated ANOVA test will be performed. To address the secondary outcome of comparison of proportion of patients with AE in the 2 groups, Chi-square test will be performed and cross-checked by generalized estimating equation (GEE) analysis. Sensitivity analysis using an intention-to-treat approach including all randomized patients will be done. A 2-tailed probability value of $p<0.05$ is considered statistically significant. Calculation will be performed using IBM SPSS Statistics Version 24 (IBM, Armonk, NY, USA).

(v) Potential pitfalls and contingency plans

There are several limitations in this study. First, consumption of NSAID and titration of csDMARDs are allowed in both groups within the 24-week study period for ethical reason and to minimize dropouts. Their usage will be recorded and adjusted in multivariable models if needed. Second, a compulsory tapering dose of prednisolone is adopted which might appear to be too early. However, it could provide important strategic data that help inform clinical practice and possibly support the therapeutic effect of very low dose prednisolone. Lastly, due to the limited duration of follow-up, the long-term efficacy and safety of short-course very low dose prednisolone could not be examined, which could be another research agenda. Additionally, conducting a randomized placebo-controlled clinical trial might meet with difficult recruitment and high drop-out, despite the relatively short study period. We intend to have a long recruitment period, screen patients in multiple centers and conservatively plan the sample size accommodating a potential higher dropout rate. Logistic issues with investigator-initiated placebo trial (e.g. production of placebo or regulatory approvals) are anticipated. The study team has secure source of placebo tablet production and experienced personnel to ensure the smooth implementation of the trial. We will also advise all the participants to have appropriate vaccinations, especially seasonal flu and COVID-19 vaccines, before entering the trial. In case of significant worsening of outbreak transmission rate or tightening of community mitigation measures, participants can be followed up at designated sites with the use of personal protective equipment, away from high risk individuals, to reduce the risk of infection. A healthy life-style with balanced diet, adequate rest and regular exercise will be recommended to every patients entering the trial.

References:

1. Lau E, Symmons D, Bankhead C, MacGregor A, Donnan S, Silman A. Low prevalence of rheumatoid arthritis in the urbanized Chinese of Hong Kong. J Rheumatol. 1993;20(7):1133-7.

2. Zhu TY, Tam LS, Li EK. Societal costs of rheumatoid arthritis in Hong Kong: a prevalence-based cost-of-illness study. Rheumatology (Oxford). 2011;50(7):1293-301.

3. Ho CTK, Mok CC, Cheung TT, Kwok KY, Yip RML. Management of rheumatoid arthritis: 2019 updated consensus recommendations from the Hong Kong Society of Rheumatology. Clin Rheumatol. 2019;38(12):3331-50.

4. Lau CS, Chia F, Dans L, Harrison A, Hsieh TY, Jain R, et al. 2018 update of the APLAR recommendations for treatment of rheumatoid arthritis. Int J Rheum Dis. 2019;22(3):357-75.

5. Fraenkel L, Bathon JM, England BR, St Clair EW, Arayssi T, Carandang K, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2021;73(7):1108-23.

6. Smolen JS, Landewé RBM, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023;82(1):3-18.

7. Dennison EM, Cooper C. Corticosteroids in rheumatoid arthritis. Bmj. 1998;316(7134):789-90.

8. Meng H, Lam SH, So H, Tam LS. Incidence and risk factors of major cardiovascular events in rheumatoid arthritis and psoriatic arthritis: A populationbased cohort study. Semin Arthritis Rheum. 2024;65:152416.

9. Kerschbaumer A, Sepriano A, Bergstra SA, Smolen JS, van der Heijde D, Caporali R, et al. Efficacy of synthetic and biological DMARDs: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2023;82(1):95-106.

10. Baoqi Y, Dan M, Xingxing Z, Xueqing Z, Yajing W, Ke X, et al. Effect of Anti-Rheumatic Drugs on Cardiovascular Disease Events in Rheumatoid Arthritis. Front Cardiovasc Med. 2021;8:812631.

11. Mok CC, So H, Yim CW, To CH, Lao WN, Wong SPY, et al. Safety of the JAK and TNF inhibitors in rheumatoid arthritis: real world data from the Hong Kong Biologics Registry. Rheumatology (Oxford). 2024;63(2):358-65.

12. Carbone F, Bonaventura A, Liberale L, Paolino S, Torre F, Dallegri F, et al. Atherosclerosis in Rheumatoid Arthritis: Promoters and Opponents. Clin Rev Allergy Immunol. 2020;58(1):1-14.

13. Waage A, Slupphaug G, Shalaby R. Glucocorticoids inhibit the production of IL6 from monocytes, endothelial cells and fibroblasts. Eur J Immunol. 1990;20(11):2439-43.

14. Joyce DA, Gimblett G, Steer JH. Targets of glucocorticoid action on TNF-alpha release by macrophages. Inflamm Res. 2001;50(7):337-40.

15. Pamukcu B, Lip GY, Shantsila E. The nuclear factor--kappa B pathway in atherosclerosis: a potential therapeutic target for atherothrombotic vascular disease. Thromb Res. 2011;128(2):117-23.

16. Makarov SS. NF-kappa B in rheumatoid arthritis: a pivotal regulator of inflammation, hyperplasia, and tissue destruction. Arthritis Res. 2001;3(4):200-6.

17. Nelson G, Wilde GJ, Spiller DG, Kennedy SM, Ray DW, Sullivan E, et al. NF-kappaB signalling is inhibited by glucocorticoid receptor and STAT6 via distinct mechanisms. J Cell Sci. 2003;116(Pt 12):2495-503.

18. del Rincón I, Battafarano DF, Restrepo JF, Erikson JM, Escalante A. Glucocorticoid

dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. Arthritis Rheumatol. 2014;66(2):264-72.
19. So H, Lam TO, Meng H, Lam SHM, Tam LS. Time and dose-dependent effect of systemic glucocorticoids on major adverse cardiovascular event in patients with rheumatoid arthritis: a population-based study. Ann Rheum Dis. 2023;82(11):1387-93.
20. Ocon AJ, Reed G, Pappas DA, Curtis JR, Kremer JM. Short-term dose and durationdependent
glucocorticoid risk for cardiovascular events in glucocorticoid-naive patients with rheumatoid arthritis. Ann Rheum Dis. 2021;80(12):1522-9.
21. Boers M, Hartman L, Opris-Belinski D, Bos R, Kok MR, Da Silva JA, et al. Low dose, add-on prednisolone in patients with rheumatoid arthritis aged 65+: the pragmatic randomised, double-blind placebo-controlled GLORIA trial. Ann Rheum Dis. 2022;81(7):925-36.
22. Buttgereit F, Mehta D, Kirwan J, Szechinski J, Boers M, Alten RE, et al. Low-dose prednisone chronotherapy for rheumatoid arthritis: a randomised clinical trial (CAPRA-2). Ann Rheum Dis. 2013;72(2):204-10.
23. Burmester GR, Buttgereit F, Bernasconi C, Álvaro-Gracia JM, Castro N, Dougados M, et al. Continuing versus tapering glucocorticoids after achievement of low disease activity or remission in rheumatoid arthritis (SEMIRA): a double-blind, multicentre, randomised controlled trial. Lancet. 2020;396(10246):267-76.
24. Pincus T, Swearingen CJ, Luta G, Sokka T. Efficacy of prednisone 1-4 mg/day in patients with rheumatoid arthritis: a randomised, double-blind, placebo controlled withdrawal clinical trial. Ann Rheum Dis. 2009;68(11):1715-20.
25. Luís M, Boers M, Saag K, Buttgereit F, da Silva JAP. The safety of glucocorticoids in the treatment of inflammatory rheumatic disease: new evidence. Curr Opin Rheumatol. 2022;34(3):179-86.
26. Strehl C, Bijlsma JW, de Wit M, Boers M, Caeyers N, Cutolo M, et al. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force. Ann Rheum Dis. 2016;75(6):952-7.
27. Wiebe E, Huscher D, Schaumburg D, Palmowski A, Hermann S, Buttgereit T, et al. Optimising both disease control and glucocorticoid dosing is essential for bone protection in patients with rheumatic disease. Ann Rheum Dis. 2022;81(9):1313-22.
28. Bijlsma JWJ. Annals of the Rheumatic Diseases collection on glucocorticoids (2020–2023): novel insights and advances in therapy. Annals of the Rheumatic Diseases. 2024;83(1):4-8.
29. So H, Cheng IT, Lau SL, Chow E, Lam T, Hung VW, et al. Effects of RANKL inhibition on promoting healing of bone erosion in rheumatoid arthritis using HRpQCT: a 2-year, randomised, double-blind, placebo-controlled trial. Ann Rheum Dis. 2021;80(8):981-8.
30. Tam LH, Shang Q, Li EK, Wong PC, Kwok KY, Kun EW, et al. Effect of Treat-totarget Strategies Aiming at Remission of Arterial Stiffness in Early Rheumatoid Arthritis: A Randomized Controlled Study. J Rheumatol. 2018;45(9):1229-39.

Table 1 – Clinical features and disease activity at baseline and week 4 of the patients treated with prednisolone 4mg daily (n=6)

	Baseline	Week 4
Age	55 ± 14	
Sex, female	4 (67%)	
Disease duration, months	4.4 ± 8.0	
RF titre, IU	68.0 ± 85.6	
Anti-CCP titre, IU	143.2 ± 90	
Tender joint count	10.5 ± 8.9	5.8 ± 11
Swollen joint count	2.5 ± 0.5	0.7 ± 1.0
ESR	63 ± 43	45 ± 37
CRP	12.0 ± 7.4	8.1 ± 9.4
DAS28-CRP	5.0 ± 0.7	3.4 ± 1.6

Anti-CCP – anti-cyclic citrullinated peptide antibody; ESR - erythrocyte sedimentation rate; CRP – C-reactive protein

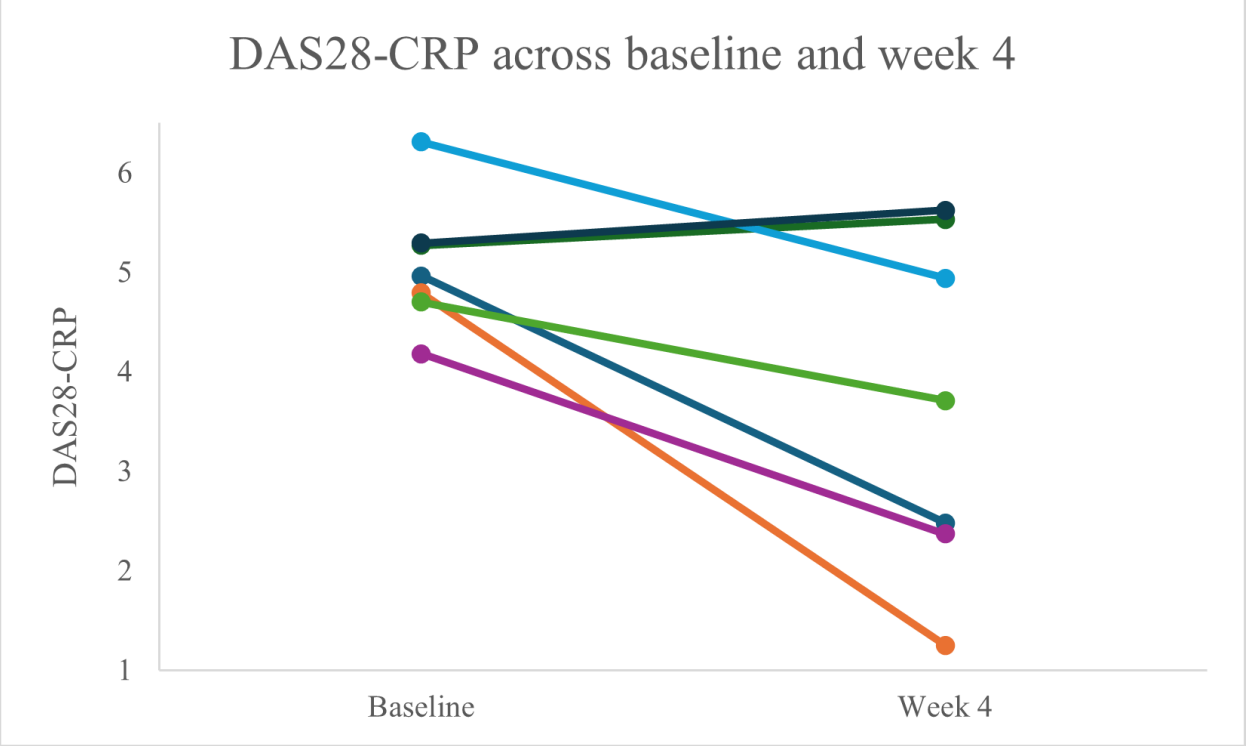
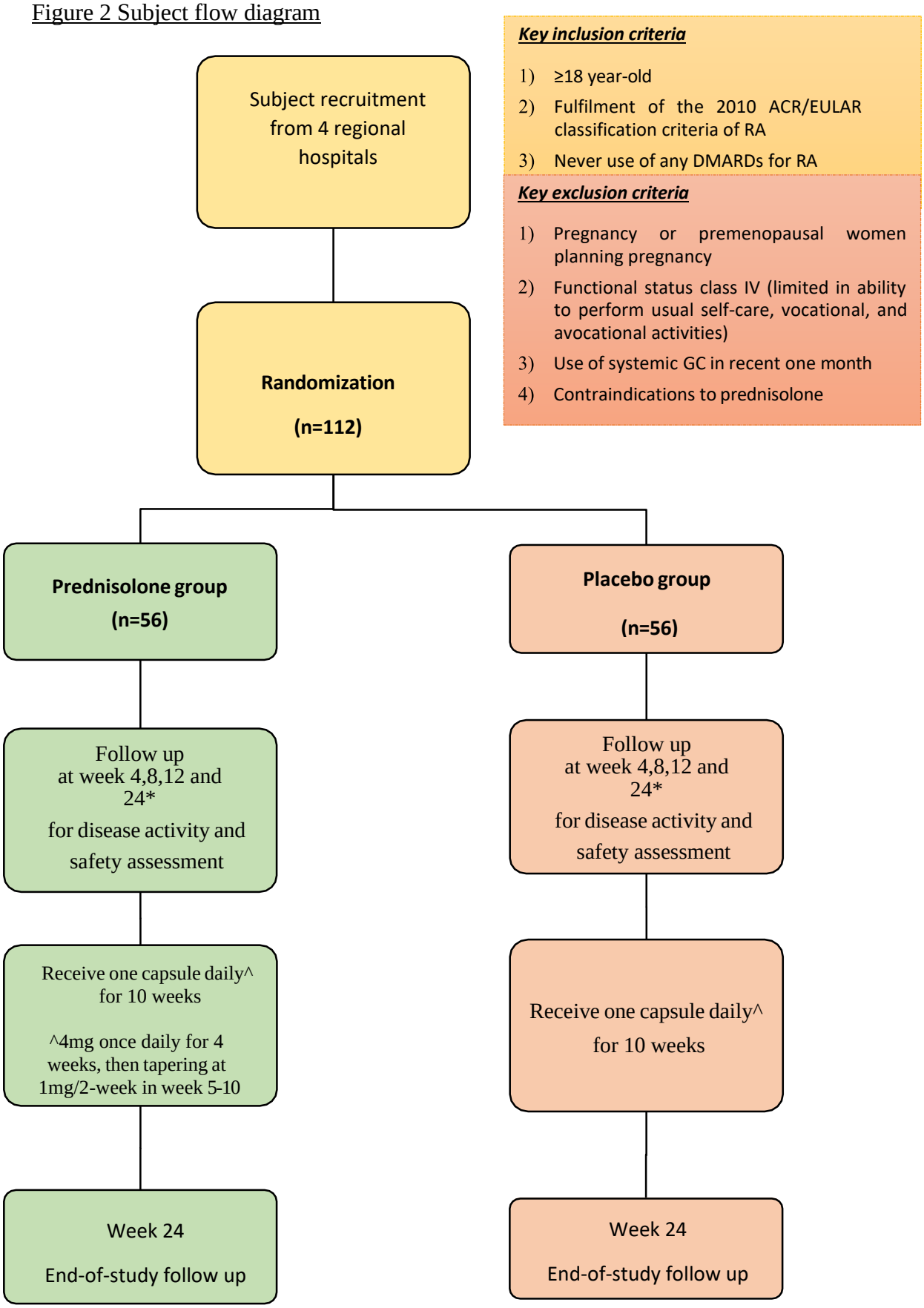


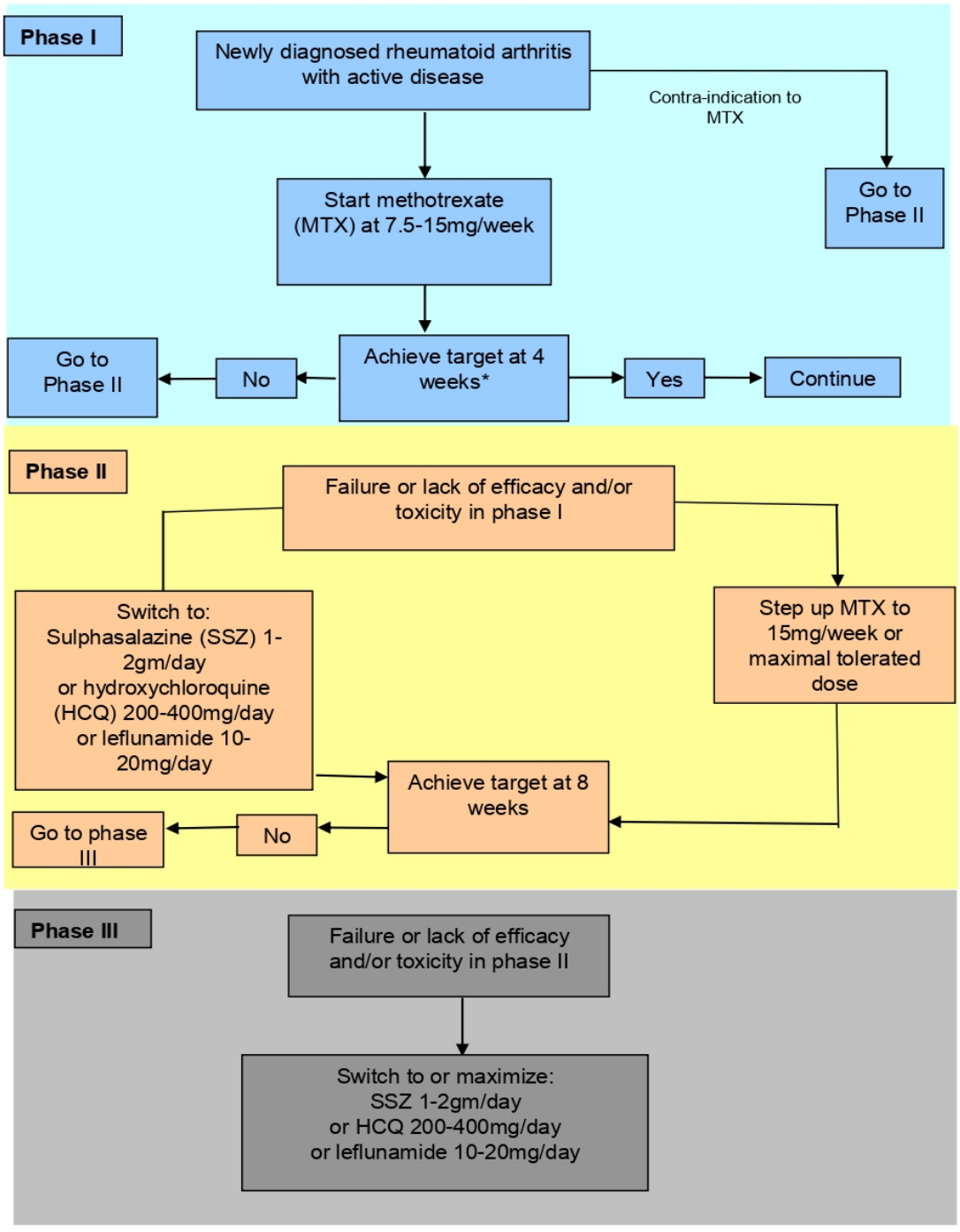
Figure 1 Change of DAS28-CRP from baseline to week-4 after prednisolone 4mg daily in patients with early RA (n=7)

Figure 2 Subject flow diagram



*Patients will be advised to reach out to the rheumatologists earlier if the condition changes unexpectedly.

Figure 3. Treatment protocol



*The treatment target is low disease activity, defined as DAS28≤3.1.