Introduction

The outlook of rheumatoid arthritis (RA) has been altered dramatically following the introduction of biologic-disease-modifying anti-rheumatic drugs (bDMARDs). The so-called biologic revolution, spearheaded by tumor necrosis factor alpha (TNF-α) antagonists, has led to unprecedented improvements in clinical, radiographic, and functional outcomes (1). Furthermore, the current goal of the RA treatment is disease remission, and biologics have been pivotal in enabling such a possibility (2). However, registry data suggest that biologic retention, necessary to achieve these aims, depends on various factors—one of which is the csDMARD co-prescription (3).

Most RA guidelines consider methotrexate (MTX) to be the anchor drug that must be utilized to achieve targeted treatment. If the disease remains uncontrolled, then further escalation of therapy to biologics warrants MTX co-prescription when tolerated (4). Hence, most randomized controlled trials (RCTs) evaluating biologics in RA tend to have MTX combined or biologic monotherapy arms. The latter group usually denotes either inadequate response to MTX or intolerance (5).

The active phase of RCTs, however, is mostly limited to 6 months (although the follow-up will be longer), thus providing evidence for efficacy only. Hence, open label extensions or real-world registry data give
better information on biologic survival (6). This is where MTX or other csDMARDs co-prescription utility is explored. However, depending on the population being studied, i.e., early versus established RA, the generalizability of findings remains limited (7).

Most studies looking at the issue of biologic retention have highlighted that comitant MTX is a positive marker for improved drug survival (8). However, it is not clear whether the dose of MTX is significant in this regard and if other csDMARDs could confer a similar benefit. Again, depending on disease duration, this relationship might be different and could have implications for routine clinical practice.

We present a real-world retrospective study to investigate whether csDMARD co-prescription improves biologic retention, and the optimal dose to preserve such response. The aim of the study is to equip clinicians managing established RA with a workable strategy and help decide the appropriate dose of csDMARD.

Methods
All patients prescribed biologic therapy for RA at our center between January 2003 and December 2017 were identified through departmental database. December 2017 was the cutoff date for data collection to allow at least a 12-month follow-up. A three-month treatment with a biologic agent was required to include the patient in the analysis to allow any early discontinuations related to adverse events. In case of rituximab, two cycles were required for inclusion. All patients where therapy had ceased, their last set of assessments required for inclusion. All patients where therapy had ceased, their last set of assessments required for inclusion. Any early discontinuations related to adverse events were included (Table 1). There was no biologic discontinuation due to adverse events in any patient. The mean age of the participants was 59.4 years (range, 24-90 years); 152 out of 198 (76%) were women. The median disease duration was 147.5 months (range, 73-213). A total of 141 subjects (71.2%) were White, and 44 (22%) of Asian and 13 (6%) of other background. The mean follow-up period was 44 months (range, 12-161, standard deviation [SD], 105.5). Distribution by antibodies revealed 41 (20.7%) participants had a double-positive [both rheumatoid factor (RF) and anti-citrullinated

Main Points
- Combination therapy of biologic with csDMARDs is generally more effective in RA.
- Prior studies suggest that perhaps 10mg weekly methotrexate is sufficient in early RA treated with biologics.
- Such data is missing in established RA.
- Our study recommends ≥20 mg weekly methotrexate provides best biologic retention rate in established RA.

Table 1. Demographics.

| Biologic monotherapy | Bio+MTX ≤7.5mg | Bio+MTX 10-17.5mg | Bio+MTX ≥20mg | Bio+csDMARD |
|----------------------|---------------|------------------|---------------|--------------|
| n=                   | 32            | 16               | 49            | 53           | 48           |
| Gender               | F 31, M 1     | F 14, M 2        | F 39, M 10    | F 33, M 20   | F 36, M12    |
| Mean age             | 64.4 yrs (40-82) | 63.1 yrs (37-90) | 61.32 yrs (31-83) | 54.18 yrs (24-85) | 55.12 yrs (39-81) |
| Ethnicity (n)        |               |                  |               |              |
| White                | 24            | 14               | 36            | 35           | 34           |
| Asian                | 5             | 2                | 8             | 17           | 10           |
| Afro-Caribbean       | 2             | 0                | 2             | 1            | 4            |
| Other                | 1             | 0                | 3             | 0            | 0            |
| Biologics (n)        |               |                  |               |              |
| TNF inhibitors       | 22            | 10               | 37            | 37           | 38           |
| Rituximab            | 1             | 1                | 3             | 2            | 1            |
| Abatacept            | 0             | 4                | 5             | 9            | 0            |
| Tocilizumab          | 9             | 1                | 4             | 5            | 9            |

| F: Female; M: Male; DAS28: disease activity score-28; Bio: biologic; MTX: methotrexate; csDMARD: conventional synthetic disease modifying anti-rheumatic drug; Ref: reference. |

Statistical analysis
Statistical analysis was conducted using the IBM SPSS Statistics version 23 software and Epi Info version 7.0 (CDC Atlanta USA). The one-way analysis of variance model for independent values was utilized to ascertain if there was a significant relationship among the four arms compared to biologic monotherapy dataset. The Mann-Whitney two-tailed U test was employed to determine the significance of relationship between the monotherapy group and other arms for all variables including disease duration, the length of biologic treatment and delta change in DAS28. Significance level was predefined at 0.05.
Table 2. Results by each arm.

|                      | Biologic monotherapy | Bio+MTX ≤7.5mg | Bio+MTX 10-17.5mg | Bio+MTX ≥20mg | Bio+csDMARD |
|----------------------|-----------------------|----------------|-------------------|---------------|-------------|
| n=                   | 32                    | 16             | 49                | 53            | 48          |
| Median disease       | 147.5 months          | 155 months     | 148 months        | 83 months     | 130 months  |
| duration             | (62-491)              | (18-310)       | (16-445)          | (15-445)      | (19-320)    |
| p                    | Ref                   | 0.86           | 0.35              | 0.002         | 0.26        |
| Median biologic      | 50.5 months           | 18 months      | 36 months         | 19 months     | 17 months   |
| duration             | (4-163)               | (4-87)         | (3-173)           | (3-189)       | (4-164)     |
| p                    | Ref                   | 0.12           | 0.39              | 0.007         | 0.008       |
| Median DAS28         | 3.17                  | 2.3            | 3.03              | 2.48          | 2.84        |
| improvement          | (0.98-5.08)           | (-0.94-4.73)   | (0.42-5.44)       | (-1.88-7.53)  | (-2.01-4.90) |
| p                    | Ref                   | 0.23           | 0.99              | 0.85          | 0.49        |

F: Female; M: Male; DAS28: disease activity score-28; Bio: biologic; MTX: methotrexate; csDMARD: conventional synthetic disease modifying anti-rheumatic drug; Ref: reference.

Peptide antibody (ACPA), 80 (40-44%) were single positive (61 were ACPA +ve and 19 RF+ve), and 77 (38.9%) patients were double negative. The median biologic duration was 28 months (4-189). The mean disease activity score 28 (DAS28) at biologic initiation was 5.7 (SD 1.98). Average comorbidities in the cohort were three with hypertension, hypercholesterolemia, and osteoarthritis being the most common. A total of 144 (73%) prescriptions were for TNF inhibitors, and 54 (27%) for non-TNF agents including abatacept (9.5%) (Orencia: BMS, New York USA), rituximab (2.5%) (Matthera: Roche, Basel Switzerland), and tocilizumab (15%) (Roactemra; Genentech, San Francisco USA).

A detailed analysis of all five groups is provided in Table 2. There was a statistically significant difference (p=0.03) in the biologic retention among the five arms. Compared to monotherapy, the data remained significant for ≥20 mg MTX and csDMARD groups; however, the biologic retention in the other two MTX arms was not significant. There was no significant relationship among the groups for DAS28 improvement (p=0.24).

All groups received a combination therapy in line with biologic commissioning guidelines with the most common agent being hydroxychloroquine used with MTX. The MTX monotherapy comprised 4/16 (25%), 12/49 (25%), and 14/53 (26%) in the ≤7.5 mg, 10-17.5 mg, ≥20 mg groups, respectively. In the csDMARD group (n=48), nine patients were prescribed hydroxychloroquine (6 received 200 mg daily, 3 received 400 mg daily), 7 received sulfasalazine (2 received 500 mg daily, 3 received 2 g daily, and 2 received 2.5 g daily), 8 received leflunomide 10 mg daily, and remaining 24 were applied the combinations of above.

**Discussion**

Biologic retention is better in patients with established RA who are prescribed a combination therapy with an optimal MTX dose (≥20 mg/week) and/or other csDMARDs. A low-to-moderate MTX dose (2.5 mg-17.5 mg/week) co-prescription does not confer similar biologic survival. However, a larger multicenter registry data analysis will be required to confirm it. To the best of our knowledge, this is the first study to demonstrate the optimum dose of MTX and/or csDMARD in improving biologic survival in patients with established RA. Clinicians should consider escalating the MTX dose to 20 mg/week or more to attain better biologic perseverance.

There is good evidence that the combination therapy with biologics is more efficient than either MTX or biologic monotherapy (9). MTX is considered the best drug in this regard, provided it is not contraindicated and tolerated well. MTX can be expected to intensify the favorable effects of biologics or reduce their adverse effects, thereby increasing the retention of both drugs. Where MTX is contraindicated, perhaps owing to comorbidities, an alternative csDMARD could play a role (10). However, with regard to biologic survival, clinical efficacy is only part of the picture (11).

Regarding biologic efficacy in early RA, the CONCERTO trial examined different doses of MTX in biologic-naïve patients with early, aggressive disease (12). The study revealed that the adalimumab combination with 10 or 20 mg/week MTX provided equivalent meaningful improvements in disease outcomes, suggesting that 10 mg/week of MTX might be the optimum dose in this group. Conversely, the MUSICA trial evaluated a similar question in established RA (13). It compared the MTX combination with adalimumab at 7.5 mg or 20 mg/week and demonstrated equivalent improvements in both arms, again implying that a low-dose MTX combination is sufficient in moderate-to-severe RA. Our results are incongruent to both studies, perhaps related to the fact that both are RCTs in contrast to our real-world study where patients had a longer disease duration, higher disease activity, and exposure to at least two csDMARDs prior to commencing biologic therapy. Second, both trials looked at disease outcomes where low-dose MTX seems to be adequate; however, our data examined the longevity of biologic therapy, and only higher-dose MTX or csDMARDs combination improved the retention rate.

Several mechanisms have been proposed for the MTX likely role in improving biologic efficacy, particularly for TNF inhibitors. First is the reduction of antidrug antibodies as demonstrated by Bartelds et al. (14). MTX helps to provide immunologic tolerance to biologics and reduce clearance of the drug via less formation of drug-antidrug immune complexes. This was also shown by the further analysis of CONCERTO trial whereby higher doses of MTX were associated with a higher adalimumab drug level and lower antidrug antibodies (15). Second, the MTX directly potentiates the effect of biologic, especially the TNF antagonists. MTX suppresses circulating IL-6 more so than TNF, suggesting that TNF inhibitors have a greater effect when used in combination with MTX than when used as monotherapy (16).

Several observational studies have showed that MTX improves biologic survival in a range of inflammatory rheumatic diseases. Negative predictors for biologic retention include female gender, concomitant corticosteroid application, a high DAS28 or health assessment questionnaire, the absence of MTX, and the number of previous biologics, while concomitant use of csDMARDs in addition to MTX was a positive predictor of drug survival (11). Baseline DAS28-ESR does not signifi-
ly influence drug retention, as shown in our study (17). The most likely explanation is that in the United Kingdom, the biologic initiation threshold stringent with the minimum DAS28 required to qualify for therapy is 5.1, indicating high disease. Hence, there is relative uniformity of the parameters at the commencement of biologic.

Our study also shows that alternative csDMARDs can improve biologic survival. It is worth noting that all patients must have had MTX to qualify for biologic therapy in the United Kingdom. If a biologic is chosen due to the MTX inadequate response, then MTX should be continued in combination with the biologic. Hence, all patients in biologic mono-therapy and alternative csDMARD group are true MTX-intolerant patients, which is a major strength of the study and akin to clinical practice. There is an argument that as part of the drug optimization program, one may decide to reduce or stop concomitant csDMARDs. However, such practice is uncommon, and its impact on biologic retention is unclear.

There are several caveats to be considered. The number of patients is relatively small, and this was a single-center retrospective study. There is the recruitment and selection bias as patients included received biologic therapies in line with strict reimbursement guidelines instead of being purely a clinical choice. In- tolerance to MTX is defined on the individual basis and treating clinician’s decision. All patients had severe disease at biologic initiation, and they may not be generalizable to health care settings where moderate disease can qualify for biologic therapy. It was not possible to undertake the regression analysis to ascertain potential confounders for the primary outcome as the sample size is small. This applied to the choice of biologic agent, as tocilizumab monotherapy, for instance, has been shown to have superior efficacy, although data on retention are unclear. Similarly, being a real-world study, differences in parameters such as age and disease duration in the five groups may have confounded the results.

In this study, comorbidities were measured to reflect the real-world nature of the cohort. However, whether such comorbidities biased treatment decision is uncertain as the sample size was small, and the escalation of therapy was protocolized. All patients required at least two csDMARDs (one of which has to be MTX at a maximum tolerated dose) for 6 months prior to being eligible for biologic therapy. Hence, comorbidities had little effect on the csDMARDs co-prescription. Nevertheless, the aim of the study is to show biologic retention in relation to concomitant csDMARDs and guide clinicians to accept that there may be a valid reason to apply a lower dose or an alternative to MTX owing to comorbidities or other factors. Hence, clinical judgment is required to determine the risks pertaining to csDMARDs against a potentially lower retention rate.

However, the strengths of this study are that the treatment choice was based on a real-world setting, and also, to the best of our knowledge, this is the first study with the ability to stratify patients in several groups with still meaningful results.

To improve biologic survival, the MTX dose should be escalated to 20 mg a week or more, and in people with MTX intolerance, csDMARDs co-prescription can be used as an alternative strategy. However, perseveration with the low-to-moderate MTX dose can lead to poorer retention rates.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Ethics Committee of Luton & Dunstable University Hospital (Decision Date: March 2, 2018, Decision Number: 9/2017- 18/Medicine/Rheumatology).

**Informed Consent:** Written informed consent was obtained from the patients who participated in this study.

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