EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2019.19048

Original Article

Does biologic survival depend on co-prescribed methotrexate dose in established rheumatoid arthritis? A real-world study

Nadira B. Mothojakan, Janki Gore, Muhammad K. Nisar

Abstract

Objective: Several seminal studies have suggested that a combination therapy of biologics with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) improve disease outcomes in rheumatoid arthritis (RA). Hence, most guidelines reflect this practice. It has also been shown that methotrexate (MTX) at a dose of 8-10 mg/week is perhaps sufficient to achieve better outcomes in early RA. However, it is not clear whether this strategy enhances biologic retention in the patients with established RA. We present a real-world retrospective study to investigate whether csDMARD co-prescription improves biologic retention and the optimal dose to preserve such response.

Materials and Methods: All patients prescribed biologic therapy for RA at our center between 2003 and 2017 were identified through the departmental database. They were split into five groups based on a weekly MTX dose (≤7.5 mg, 10-17.5 mg, ≥20 mg), other csDMARD prescription, or biologic monotherapy. The one-way analysis of variance model for independent values was utilized to ascertain the significance of data. The Mann-Whitney two-tailed U test was employed to determine the significance of relationship between the monotherapy group and other arms. The significance level was predefined at 0.05.

Results: A total of 168 patients with 198 biologic events were included. The mean age was 59.4 years (range, 24-90 years). 78% were women. The mean disease duration was 155.6 months (range, 15-491). There was a statistically significant difference (p=0.03) in 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 groups for DAS28 improvement (p=0.24).

Conclusion: Our results suggest that to improve biologic retention, the MTX dose should be increased to 20 mg a week or more, and, in people with MTX intolerance, csDMARDs co-presciption can be an alternative strategy. Maintenance with a low-to-moderate MTX dose can lead to poorer retention rates.

Keywords: Rheumatoid arthritis, biologic, survival, retention, methotrexate

ORCID ID of the corresponding author:
M.K.N. 0000-0002-5132-3972.

Cite this article as: Mothojakan N, Janki G, Nisar M. Does biologic survival depend on co-prescribed methotrexate dose in established rheumatoid arthritis? Eur J Rheumatol 2020; 7(1): 21-5.

Department of Rheumatology, Luton & Dunstable University Hospital NHSFT, Luton, UK

Address for Correspondence:
Muhammed Nisar; Department of Rheumatology, Luton & Dunstable University Hospital NHSFT, Luton, UK

E-mail: drnisar12@yahoo.co.uk

Submitted: March 29, 2019
Accepted: June 28, 2019
Available Online Date: November 25, 2019

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 concomitant 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 were carried forward to final analysis. The last dataset available by December 2017 was included for those continuing therapy. Up to 3 months of temporary interruptions were allowed for clinical reasons. However, any longer breaks in therapy were considered as new drug events.

Patients with established RA (defined by the 1987 revised criteria of the American College of Rheumatology with disease duration >1 year at the time of biologic initiation) were included. If a person underwent more than one biologic course, it was counted as a separate biologic event. In accordance with commissioning guidelines, no patient can have biologic treatment unless his or her DAS28 is >5.1, despite an adequate trial of two csDMARDs over 6 months. It allowed csDMARD doses taken at the point of initiation of biologic therapy to be included for analysis as the patients would be well established on a fixed dose at that juncture.

Participants were split into five groups based on a weekly MTX dose (≤7.5 mg, 10-17.5 mg, ≥20 mg), other csDMARD prescription, or biologic monotherapy. The monotherapy arm was considered the control arm and included patients who were intolerant to MTX, and at least one alternative csDMARD.

The project was approved on March 2, 2018 (approval number 9/2017-18/Medicine/Rheumatology).

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.

Results

A total of 168 patients with 198 biologic 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

Table 1. Demographics.

	Biologic monotherapy	Bio+MTX ≤7.5mg	Bio+MTX 10-17.5mg	+MTX Bio ≥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.

Main Points

- Combination therapy of biologic with cDMARDs 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 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 duration	147.5 months (62-491)	155 months (18-310)	148 months (16-445)	83 months (15-445)	130 months (19-320)
p	Ref	0.86	0.35	0.002	0.26
Median biologic duration	50.5 months (4-163)	18 months (4-87)	36 months (3-173)	19 months (3-189)	17 months (4-164)
p	Ref	0.12	0.39	0.007	0.008
Median DAS28 improvement	3.17 (0.98-5.08)	2.3 (-0.94-4.73)	3.03 (0.42-5.44)	2.48 (-1.88-7.53)	2.84 (-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 (40.4%) 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%) (Mabthera: 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 significant-

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 monotherapy 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. Intolerance 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-presciption 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.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.K.N.; Design - M.K.N.; Supervision - M.K.N.; Resources - J.G., N.B.M.; Materials - J.G., N.B.M.; Data Collection and/or Processing - J.G., N.B.M.; Analysis and/ or Interpretation - N.B.M., M.K.N.; Literature Search - N.B.M., M.K.N.; Writing Manuscript - N.B.M., J.G., M.K.N.; Critical Review - M.K.N.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Nisar MK, Östör AJK. The role of Tumour Necrosis Factor-α in the treatment of rheumatoid arthritis- a review. Eur Musculoskeletal Rev 2011; 6: 174-8.
2. Nisar MK, Östör AJK. Disease remission the goal of therapy in rheumatoid arthritis. Practitioner 2010; 254: 17-21.
3. Gabay C, Reik M, Scherer A, Finchk A, SCQM collaborating physicians. Effectiveness of biologic DMARDs in monotherapy versus in combination with synthetic DMARDs in rheumatoid arthritis: data from the Swiss Clinical Quality Management Registry. Rheumatology (Oxford) 2015; 54: 1664-72. **[CrossRef]**
4. Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017; 76: 960-77. **[CrossRef]**
5. Hazelwood GS, Barnabe C, Tomlinson G, Marshall D, Devoe D, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying antirheumatic drugs for rheumatoid arthritis: abridged Cochrane systematic review and network meta-analysis. BMJ 2016; 353: i1777. **[CrossRef]**
6. Hetland ML, Lindegaard HM, Hansen A, et al. Do changes in prescription practice in patients with rheumatoid arthritis treated with biological agents affect treatment response and adherence to therapy? Results from the nationwide Danish DANBIO Registry. Ann Rheum Dis 2008; 67: 1023-6 **[CrossRef]**
7. Gomez-Reino JJ, Rodriguez-Lozano C, Campos-Fernandez C, et al. Change in the discontinuation pattern of tumour necrosis factor antagonists in rheumatoid arthritis over 10 years: data from the Spanish registry BIOBADASER 2.0. Ann Rheum Dis 2012; 71: 382-5 **[CrossRef]**
8. Inui K, Koike T. Combination therapy with biologic agents in rheumatic diseases: current and future prospects. Ther Adv Musculoskelet Dis 2016; 8: 192-202. **[CrossRef]**
9. Zhang J, Xie F, Delzell E, Yun H, Lewis JD, Haynes K, et al. Impact of biologic agents with and without concomitant methotrexate and at reduced doses in older rheumatoid arthritis patients. Arthritis Care Res (Hoboken). 2015; 67: 624-32. **[CrossRef]**
10. Singer O, Gibofsky A. Methotrexate versus leflunomide in rheumatoid arthritis: what is new in 2011? Curr Opin Rheumatol 2011; 23: 288-92. **[CrossRef]**
11. Ebina K, Hashimoto M, Yamamoto W, Ohnishi A, Kabata D, Hirano T, et al. Drug retention and discontinuation reasons between seven biologics in patients with rheumatoid arthritis -The ANSWER cohort study. PLoS One 2018; 13: e0194130. **[CrossRef]**
12. Burmester GR, Kivitz AJ, Kupper H, Arulmani U, Florentinus S, Goss SL, et al. Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. Ann Rheum Dis 2015; 74: 1037-44. **[CrossRef]**
13. Kaeley G, Evangelisto A, Nishio M, Liu S, Kupper H. Impact of methotrexate dose reduction upon initiation of adalimumab on clinical and ultrasonographic parameters in patients with moderate to severe rheumatoid arthritis. Ann Rheum Dis 2014; 73: 238. **[CrossRef]**

14. Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, Dijkmans BA, Tak PP, Wolbink GJ. Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. Ann Rheum Dis. 2007; 66: 921-6. **[CrossRef]**
15. Goss SL, Klein CE, Jin Z, Locke CS, Rodila RC, Kupper S, Burmester G, Awni WM. Methotrexate Dose in Patients With Early Rheumatoid Arthritis Impacts Methotrexate Polyglutamate Pharmacokinetics, Adalimumab Pharmacokinetics, and Efficacy: Pharmacokinetic and Exposure-response Analysis of the CONCERTO Trial. Clin Therap 2018; 40: 309-19. **[CrossRef]**
16. Nishina N, Kaneko Y, Kameda H, Kuwana M, Takeuchi T. Reduction of plasma IL-6 but not TNF-α by methotrexate in patients with early rheumatoid arthritis: a potential biomarker for radiographic progression. Clin Rheumatol 2013; 32: 1661-6. **[CrossRef]**
17. Souto A, Maneiro JR, Gomez-Reino JJ. Rate of discontinuation and drug survival of biologic therapies in rheumatoid arthritis: a systematic review and meta-analysis of drug registries and health care databases. Rheumatology (Oxford). 2016; 55: 523-34. **[CrossRef]**