

Original Article

Drug-survival profiling of second-line biologic therapy in rheumatoid arthritis: Choice of another TNFi or a biologic of different mode of action?

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Running title –

Drug-survival profiling of second-line biologics in rheumatoid arthritis.

Abstract:

Objectives:

Aiming to assess the best choice of second-line therapy between second-line TNF-inhibitor (TNFi) and biologics of different mode of action (BDMA-rituximab/tocilizumab/abatacept) in rheumatoid arthritis (RA) by assessing their drug-survival spanning more than 10 years, after discontinuation of the first-line TNFi.

Methods

This retrospective-observational drug-survival study was performed across 2-different hospitals in UK by conventional-statistics and machine-learning approach.

Results:

From a total of 435-patients, 213 [(48.9%); TNFi-n=122 (57.3%), BDMA-n=91(42.7%)] discontinued their second-line biologic [median-drug-survival: TNFi-27months (95%CI 22-32months) vs BDMA-37months (95%CI 32-52months)]. As second-line, BDMA was likely to reduce the risk of treatment-discontinuation [Hazard-ratio/HR-0.63 (95%CI 0.48-0.83)] compared to TNFi, but only in seropositive-patients [HR-0.52 (95%CI 0.38-0.73)], not in seronegative-RA. Uncovered by the survival-tree and adjusted by propensity-score, drug-survival benefit of BDMA over TNFi was not observed if the seropositive-patients were previously exposed to monoclonal-TNFi (HR-0.77, 95% CI 0.49-1.22) versus soluble TNFi (etanercept or its biosimilar) or if first-line TNFi was terminated within 23.9months of initiation (HR-0.97, 95%CI 0.56-1.68).

Conclusion:

BDMA, as second-line biologic, is more likely to be sustained in seropositive-patients particularly if they were previously not exposed monoclonal TNFi. Drug-survival benefit of BDMA was not observed in seronegative-patients or if the first-line TNFi was stopped within 2 years.

Key Messages:

1. BDMA is a potential preferential second-line therapy in seropositive-RA as opposed to another TNFi.
2. Drug-survival benefit of BDMA in seropositive-patients was not found if treated with monoclonal-TNFi (not etanercept) as first-line.
3. Seronegative-patients/patients terminating first-line-TNFi within 2 years did not show drug-survival benefit of BDMA over TNFi.

Key words: Rheumatoid arthritis, TNF inhibitor, Rituximab, Abatacept, Tocilizumab.

Abbreviations: *BDMA = Biologics of different mode of action, csDMARDs = conventional synthetic Disease modifying anti-rheumatic drugs, TNFi = Tumour necrotic factor-inhibitor.*

INTRODUCTION:

Biologics are increasingly used as part of the standard of care in rheumatoid arthritis (RA) after failure of initial conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). Among the biologics, tumour necrosis factor inhibitors (TNFi) are the most widely used as first-line therapy. Approximately 30% of patients do not respond to the first-TNFi (1) (primary-failure), and among those who have shown initial response, almost half experience loss of efficacy (secondary-failure) within 5-years (2). In the event of failure, the options are switching to another TNFi or biologics of different mode of action (BDMA). Several studies have demonstrated good clinical response after switching to another TNFi, however, the efficacy was lower compared to the first-line TNFi (3-5). Switching to a second TNFi was deemed to be more successful when the first-line TNFi was ceased due to intolerance or secondary-failure compared to primary-failure (3-4). Swapping to BDMA, after TNFi failure has been supported by few randomised placebo-controlled trials (3-5) favouring its use as second-line therapy (6, 7); although others failed to demonstrate this (8). Seropositive-RA patients follow a distinct clinical pattern (9) and previously it has been shown to have a negative influence on drug-survival (10), however little is known if the seropositivity can influence the retention and efficacy of the second-line therapy. Indeed, long term drug-survival comparing TNFi and BDMA as second-line, has surprisingly been less investigated.

Here we present drug-survival of second-line biologics in RA-patients. The primary objective was to assess the best choice of second-line biologic therapy after discontinuation [due to primary- or secondary-failure, and adverse drug-reactions (ADRs)] of the first-line TNFi through evaluating drug-survival by depicting discontinuation of second-line biological treatment. We also aimed to profile them by the major determinants influencing the drug-retention of second-line therapy.

METHODS:

Study-population and outcome

A real-world data analysis was performed on RA-patients (according to 1987 or 2010 ACR/EULAR classification criteria) (11), who had been started on second-line TNFi (or biosimilars) or a BDMA (rituximab or its biosimilar/tocilizumab/abatacept) from February2007 to March2018 from two independent-hospitals of North-East London. Data were extracted in November2019. In both hospitals, patients were treated under the National Institute of Clinical Excellence (NICE) guidelines (12). For RA, continuation of biologics treatment is only allowed if Disease Activity Scores based on 28 joint-counts (DAS28) show at least a moderate-response by

6 months (primary-failure = lack of efficacy in first 6 months). After the initial-response, treatment must be discontinued if the response is not maintained or if ADRs occur. Therefore, continuation of biologics can act as a surrogate of sustained efficacy and safety. Patients initiated on a second-line biologics therapy after withdrawal of the first-line TNFi (primary/secondary-inefficacy, or ADRs) were included. Patients were right-censored (13) if the treatment was discontinued due to other reasons like – pregnancy, remission, lost follow-up, or moved away (14).

Baseline data

Demographics and disease characteristics at the time of initiation of second-line biologics-therapy [age, gender, disease-duration, duration of first-line TNFi, cause of cessation of initial-TNFi, DAS28-ESR (erythrocyte sedimentation rate), swollen and tender joint-count, patients' visual analogue score (VAS), C-reactive protein (CRP), ESR, and seropositivity (either rheumatoid-factor/RF or anti-citrullinated peptide/ACPA antibodies)], concomitant use of prednisolone and csDMARDs were recorded. Second-line biologics were TNFi [soluble receptor blocker- etanercept (or biosimilars), and monoclonal antibodies (-mabs) – adalimumab (or biosimilars), certolizumab, infliximab, or golimumab] and BDMA (rituximab, tocilizumab, abatacept). Any given combination therapy of TNFi with methotrexate (or other csDMARDs) was determined if they were already taking the csDMARDs and continued it following the TNFi initiation. Patients on combination therapy were right-censored in the survival analysis if they discontinued the csDMARDs (15). Similarly, monotherapy initiators were also right-censored if csDMARD(s) were added later.

Statistical analysis

Statistical analysis was performed using R software version 4.0.2 for Mac OS (R Foundation for Statistical Computing, Vienna, Austria). Multiple imputation by Markov chain Monte Carlo equations under the missing-at-random assumption were used for missing values of covariates (exact numbers-Supplementary Table 1). Forty-datasets were imputed, analysed, and pooled using Rubin's rules (16) by *mice* (17) package.

Kaplan-Meier (K-M) analysis and propensity-score adjusted cox-regression were used to analyse time to treatment-discontinuation. Propensity-score were estimated for each patient using logistic-regression with treatment as the dependent variable and adjusted for age, disease duration, duration of first-line biologics used, cause of discontinuation of first-line biologics, type of first-TNFi, gender, antibody-status, concomitant

csDMARDs with baseline tender and swollen joint count, patients' global-VAS, DAS28-ESR, and CRP. We further adopted machine-learning technique, survival-tree, using *rpart* (18) package which was constructed by growing the initial tree by binary-splitting and then pruning the tree to terminal-nodes with log-rank. To verify the results of survival-tree, multivariate cox-regression was used to determine important covariates to predict treatment-discontinuation, where the variables were chosen by elastic-net (19) regression.

Ethics approval

This analysis was done as part of a service evaluation of clinical care. According to National Health Service (NHS) Research Ethics Committee guidelines, no formal ethical approval was required.

RESULTS:

Second-line BDMA showed longer drug-retention time compared to TNFi

A total of 435-patients were included from 2-cohort (Figure 1). The mean age was 46.6years (SD11.7), with over 70% of female predominance (Table 1). Three-quarters of the patients were seropositive. Half of them used etanercept as first-line (Table 1), and 68% of the etanercept treated patients (144/211) were switched to BDMA, whereas 32% (28/88) and 31% (27/86) of adalimumab and infliximab treated patients were switched to BDMA, respectively (Supplementary Figure 1).

BDMA prolonged the time of drug-survival (Figure 2A) with median-time of discontinuation of 37months (95%CI 32-52) and hazard-ratio (HR) of 0.63 (95%confidence interval/95%CI 0.48-0.83) compared to TNFi [median-time 27months (95%CI 22-32)]. Drug-survival benefit of BDMA was observed irrespective of the cause of cessation of first-line TNFi [primary (HR-0.56, 95%CI 0.33-0.96) and secondary-failure (HR-0.65, 95%CI 0.47-0.93)] (Supplementary Figure 2A-B), unless discontinued due to ARDs (Supplementary Figure 2C).

Propensity-score matched sensitivity analysis also demonstrated the better endurance of BDMA over TNFi (HR-0.62, 95%CI 0.46-0.84) (Figure 3A). Among the BDMA(s) – rituximab and abatacept showed longer persistence with HR-0.55 (95%CI 0.38-0.81) and 0.63 (95%CI 0.40-0.91), respectively, compared to TNFi. Unadjusted HRs of treatment-discontinuation of different TNFi and BDMA(s) are shown in Supplementary Table 1. We further sought to analyse the difference in drug-survival among these 3 BDMA(s), which suggested an identical drug-survival rate (Supplementary Figure 3A).

Drug-survival analysis by their antibody-status illustrated BDMA was associated with reduced withdrawal risk, compared to TNFi, in seropositive-patients (HR-0.52, 95%CI 0.38-0.73) (Figure 2B); which was further confirmed by propensity-score matched sensitivity-analysis (Figure 3B, unadjusted HRs in Supplementary Table 2). Along with having comparable intra-group drug-survival rates of these 3-BDMA(s) in seropositive RA patients (Supplementary Figure 3B), all were associated with longer drug-survival in seropositive-patients [rituximab (HR-0.45, 95%CI 0.29-0.72), abatacept (HR-0.51, 95%CI 0.30-0.86), and tocilizumab (HR-0.56, 95%CI 0.38-0.73)] compared to TNFi (Figure 3B). Further analysis of patients who were seropositive to both RF and ACPA (not only to either of them) also revealed the drug-survival benefit of BDMA (Figure 2C) over TNFi. In contrast, BDMA use was not associated with a beneficial effect on treatment-retention in seronegative-patients (Figure 2D, Supplementary Table 3).

We next contrasted drug-survival between seropositive and seronegative RA patients amid the 3-BDMA(s). In combination, they illustrated favourable endurance in seropositive patients (unadjusted HR 0.52, 95%CI 0.33-0.81) over seronegative RA. While rituximab showed a tendency to be retained longer in seropositive patients (HR 0.47, 95%CI 0.21-1.07) compared to seronegative, abatacept and tocilizumab failed to yield a significant survival benefit in seropositive patients compared to seronegative patients (Supplementary Figure 4).

Drug-survival was further illustrated by the causes they were withdrawn from: primary- or secondary-failure and ADRs. A reduced withdrawal rate of BDMA (HR-0.61, 95%CI 0.46-0.88 compared to TNFi) was only observed if the treatment was ceased after 6 months (either secondary-failure or ADRs), not if discontinued due to primary-inefficacy or ADRs within 6 months (Supplementary Figure 5A-B).

Profiling the covariates related to drug-survival of BDMA and TNFi

In our survival-tree model, the terminal-nodes (Figure 4A) were split based on types of treatment [BDMA versus TNFi], age at initiation of second-line therapy (>75years versus ≤75years, splitting was based to minimise the Gini impurity), antibody-status, type (etanercept versus -mabs), and duration (<23.9months versus ≥23.9months, splitting was based to minimise the Gini impurity) of previous-TNFi. Most sustainable drug-survival was observed in elderly patients (>75 years) treated who were treated with BDMA (node-1), however, this number was too small. Seropositive BDMA-treated patients with previous monoclonal-TNFi exposure (node-3) or if

they were seronegative (node-4) showed poorer drug-survival (Figure 4A-B) compared to seropositive-patients who previously had etanercept (node-2) with HR-2.71 (95%CI 1.65-4.43) and 2.86 (95%CI 1.77-4.62), respectively. Patients treated with another TNFi, following the discontinuation of first-line TNFi, experienced less withdrawal (HR-2.06, 95%CI 1.34-3.17) if the prior-TNFi was discontinued within 23.9months after initiation (node-5) compared to those whose first-line TNFi was terminated after 23.9months (node-6). Notably, node-5 TNFi patients did not imply poorer drug-survival over a sub-group of BDMA-treated patients (node-3 and node-4) (Figure 4A-B).

The important association of the variables chosen by the survival-tree was further confirmed by elastic-net regression which was adopted to select influential variates to predict the treatment-discontinuation in BDMA and TNFi groups, separately (Supplementary Figure 6). While Seropositivity implied a favourable effect on BDMA-survival (adjusted HR-0.38, 95%CI 0.22-0.66), but seropositive-group with previous exposure to monoclonal-TNFi was associated with an increased withdrawal rate (HR-2.79, 95%CI 1.08-5.11) (Supplementary Figure 6A). This interaction of antibody-status and type of previous-TNFi (in BDMA- patients) were further adjusted by propensity-score (Supplementary Figure 6B) – yielding a similar result. In TNFi-group, for every one-year increment of treatment duration of previous-TNFi the risk of treatment-withdrawal increased by 18% (95%CI 7%-31%) (Supplementary Figure 6C).

The impact of type and duration of previous TNFi, shown in the survival-tree model, promoted us to compare drug-survival of BDMA and TNFi stratified by these variables and adjusted by propensity-score. Persistence of drug-survival, facilitated by BDMA was only retained if they were previously treated with etanercept (HR-0.49, 95%CI 0.30-0.82) (Figure 5A). Discontinuation of first-line TNFi within 23.9months also blunted the beneficial effect of BDMA on drug-survival (Figure 5A).

DISCUSSION:

Our results have uncovered a distinct clinical phenotype of patients likely to show a potential therapeutic advantage with BDMA compared to TNFi. BDMA showed longer drug-sustainability compared to TNFi when used as second-line therapy in RA patients after discontinuation of first-line TNFi resulted from loss of efficacy; This difference was more striking in seropositive-RA patients. In contrast, seronegative-patients did not show any advantage in drug-survival with BDMA. Among BDMA(s), all 3 demonstrated drug-survival benefit over

TNFi in seropositive-RA patients. Indeed, drug-survival was better in seropositive-group compared to seronegative patients, when 3 of the BDMA(s) were analysed together. Additionally, our data hinted a prolonged drug-survival in rituximab treated seropositive patients in contrast to seronegative group, which is consistent with previous study (20, 21). Unlike rituximab, impact of seropositivity on long term drug-survival of abatacept are conflicting (20, 21) and our results showed it was unaffected. Of relevance, the number of observed patients in this group was rather small. Surprisingly we found BDMA treated seropositive-patients demonstrated poorer drug-survival if treated with monoclonal-TNFi as first-line, compared to etanercept. In contrast, BDMA survival was not better to TNFi, if the duration of first-line TNFi was less than 23.9months, implying that, in addition to the antibody-status, the timing of switching is an important factor influencing the response to second-line biologic therapy.

Failure and even adverse effects have shown to be related to the immunogenicity to the TNFi and the production of anti-TNFi antibodies (ATA) resulting in a higher number of patients leading to drug-withdrawal (22). Unfortunately, under NHS care, measurement of ATA is not routinely available therefore is not possible to associate ATA production and the choice of second-line therapy. Discrepancies among the above-mentioned published data can be largely due to the distinctive immunogenic profiling of the patients who might have developed ATA. In fact, seropositive-patients were shown to have higher ATA values (23), and this could be a reason why this population showed better survival to BDMA. Moreover, our data suggest second-line TNFi survival can be affected by the duration of treatment of previous-TNFi, suggesting a possible role of potential immunogenic change over time to explain the variance of response of second-line therapy. Previous reports suggested, albeit the majority of the patients start developing ATA formation in the first six months (24), however, its titre continues to rise until the observed 2 years (25) supporting the notion of developing a significant titre of ATA following exposure to first-line TNFi over 2 years. Furthermore, ATA to first-line TNFi can augment formation of ATA to their second-line TNFi ultimately leading to discontinuation of second-line TNFi (26) and thus favouring the use of BDMA following discontinuation of first-line TNFi after 2 years of initiation. Surprisingly BDMA retention was better when patients were not previously exposed to monoclonal-TNFi which is considerably more immunogenic than etanercept. It remains unclear whether the production of ATA to these monoclonal TNFs could alter memory B-/T-cells or follicular T-helper cells which could trigger the production of ATA to BDMA(s) or whether this group of patients was genetically susceptible to ATA production.

We have analysed a large pool of RA-patients from two hospital settings with similar treatment standards in adherence to the NICE guidelines. The choice of the two different hospitals was random and enabled us to generalise our findings. We acknowledge this was a retrospective study with all the inherent weaknesses of such a methodology. Records of intra-muscular and intra-articular corticosteroids were not available which may impact short-term response but is unlikely to have any effect on long-term survival and the decision to change therapy. Confounders such as smoking, obesity, alcohol, and exercise were also not available. Additionally, adherence to both methotrexate and TNFi may be a key determinant factor that is difficult to measure.

In conclusion, our study supports the potential therapeutic advantage of BDMA as a second-line therapy by improving drug-survival in seropositive-patients with RA. Drug-survival of BDMA can be reduced by previous exposure to monoclonal-TNFi in seropositive-patients, indicating a role in altering the underlying immunological process. Either BDMA or a TNFi can be chosen in seronegative-RA, seropositive-RA patients with previous exposure to monoclonal-TNFi, or if the duration of first-line TNFi was less than 2 years. Further prospective studies are required to confirm these findings along with research including the measurement of ATA to explore immunogenic changes after the failure of initial TNFi.

Conflict of interest None.

Contributors MS, NAN, MM were involved in data collection. MS and MDC performed statistical analysis. MS, MDC, EB, NV, DM, and ER were involved in the design of the study design and data interpretation. All authors contributed and reviewed the manuscript's content before submission.

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Data availability statement: Anonymised individual patient data will be shared upon reasonable request for research purposes.

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Table 1: Baseline characteristics of patients with rheumatoid arthritis who started a second-line biologics following discontinuation of first-line tumour necrotic factor inhibitor.

Characteristics	Second TNFi ^a	BDMA ^b
	N = 209 ¹	N = 226 ¹
Age at initiation of second biologics, years	46 (12)	47 (10)
Female	150 (72%)	160 (71%)
Disease duration at initiation of second TNFi, years	9 (11)	7 (7)
Duration of efficacy of first biologics, months	49 (23)	48 (25)
Reason for cessation of first biologics		
Primary failure	59 (28%)	49 (22%)
Secondary failure	125 (60%)	153 (68%)
Adverse effect or intolerance	25 (12%)	24 (11%)
Seropositive patients	154 (74%)	182 (81%)
Missing value, n	6	1
DAS28-ESR at baseline	6.34 (0.70)	6.92 (0.99)
Missing value, n	27	13
Swollen joint count at baseline	9 (5)	14 (6)
Missing value, n	47	33
Tender joint count at baseline	10 (6)	18 (5)
Missing value, n	56	51
C-Reactive protein at baseline	16 (16)	21 (14)
Missing value, n	44	14
Observed period, months		
Mean (SD)	23.1 (17.5)	24.3 (17.3)
Median (IQR)	20 (11-32)	21 (12-32)
Concomitant csDMARDs ^c		
Concomitant methotrexate	74 (35.4%)	111 (49.1%)
Concomitant sulfasalazine	32 (15.3%)	31 (13.7%)
Concomitant leflunomide	42 (20.1%)	13 (5.8%)
Concomitant oral prednisolone	34 (16.3%)	21 (9.3%)
Number of previous csDMARDs		
1	7 (3.3%)	22 (9.7%)
2	153 (73%)	132 (58%)
3	37 (18%)	59 (26%)
4	12 (5.7%)	13 (5.8%)
Previous (first line) TNFi		
Etanercept	67 (32%)	144 (64%)
Adalimumab	60 (29%)	28 (12%)
Infliximab	59 (28%)	27 (12%)
Certolizumab	12 (5.7%)	16 (7.1%)
Golimumab	11 (5.3%)	11 (4.9%)

¹ Mean (SD); n/N (%).^a TNFi = Tumour necrotic factor inhibitor, ^b BDMA = Biologics of different mode of action, ^c csDMARDs = conventional synthetic Disease modifying anti-rheumatic drugs

Figure Legends

Figure 1: Study population.

Patients who discontinued due to remission, pregnancy, moved away, or lost in follow-up were right censored.

BDMA = Biologics of different mode of action, TNFi = Tumour necrotic factor inhibitor.

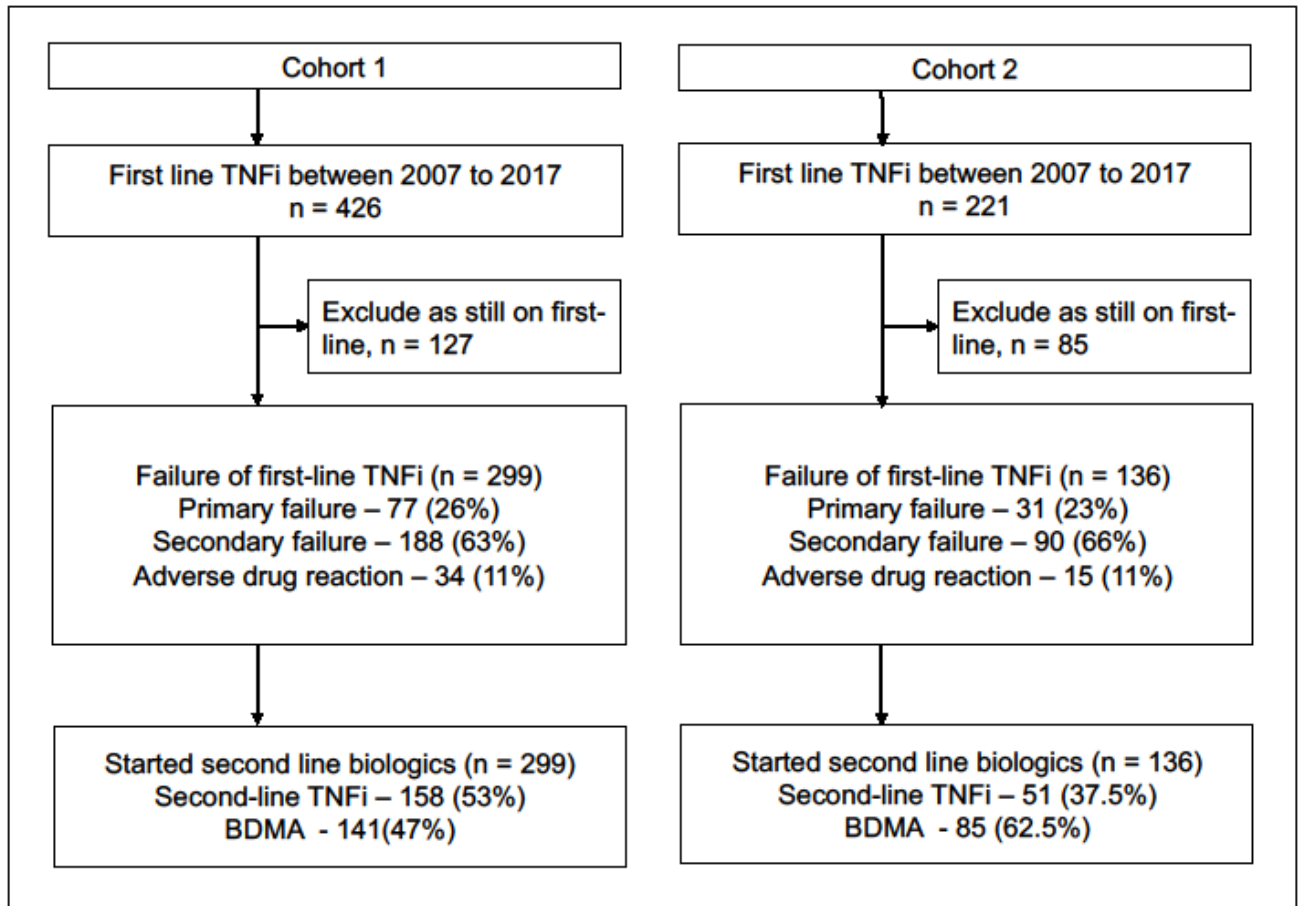


Figure 2 A-B: Comparison between TNFi (Tumour necrotic factor inhibitor) and BDMA (Biologics of different mode of action) as second-line therapy in rheumatoid arthritis (RA) patients after discontinuation of first-line TNFi. Kaplan-Meier (KM) survival analysis of time to treatment discontinuation - stratified by TNFi and BDMA in (A) all patients, (B) seropositive RA – positive to either rheumatoid-factor (RF) or anti-citrullinated peptide antibody (ACPA), (C) seropositive RA – positive to both RF/ACPA, and (D) seronegative RA – negative to both RF/ACPA.

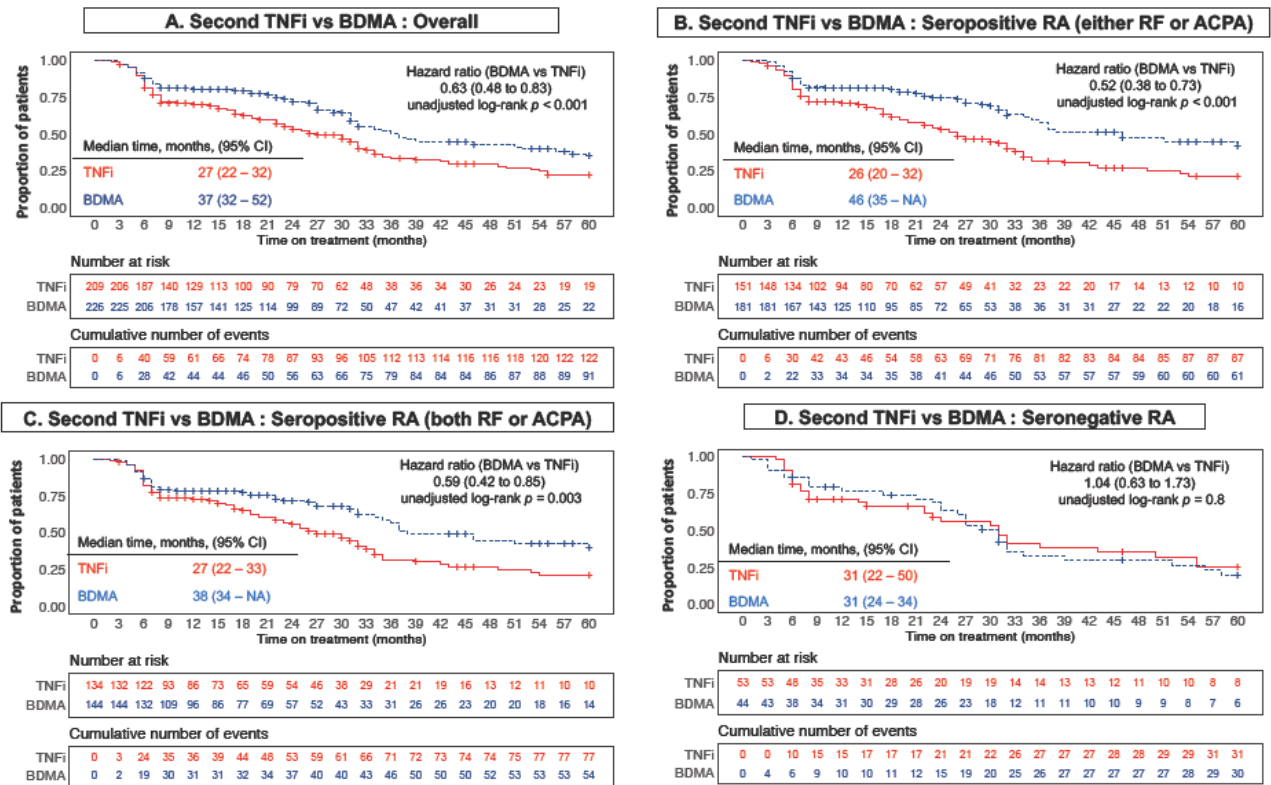


Figure 3 A-B: Comparison between TNFi (Tumour necrotic factor inhibitor) and BDMA (Biologics of different mode of action) as second-line therapy in rheumatoid arthritis (RA) patients after discontinuation of first-line TNFi (adjusted by propensity quintile score[†]). Hazard ratio (HR) [with 95%Confidence interval (CI)] of discontinuation of second-line biologics therapy in RA patients - in (A) all patients, (B) seropositive RA – positive to either rheumatoid-factor (RF) or anti-citrullinated peptide antibody (ACPA).

[†] Propensity quintile was adjusted for age of initiation of second biologics, disease duration at the initiation of second biologics, duration of first biologics, cause of discontinuation of first biologics, sex, baseline disease activity score (DAS28-ESR), c-reactive protein at baseline, tender and swollen joint count at baseline, patients' global VAS, Erythrocyte sedimentation rate (ESR) at baseline, concomitant use of conventional synthetic disease-modifying anti-rheumatic drugs.

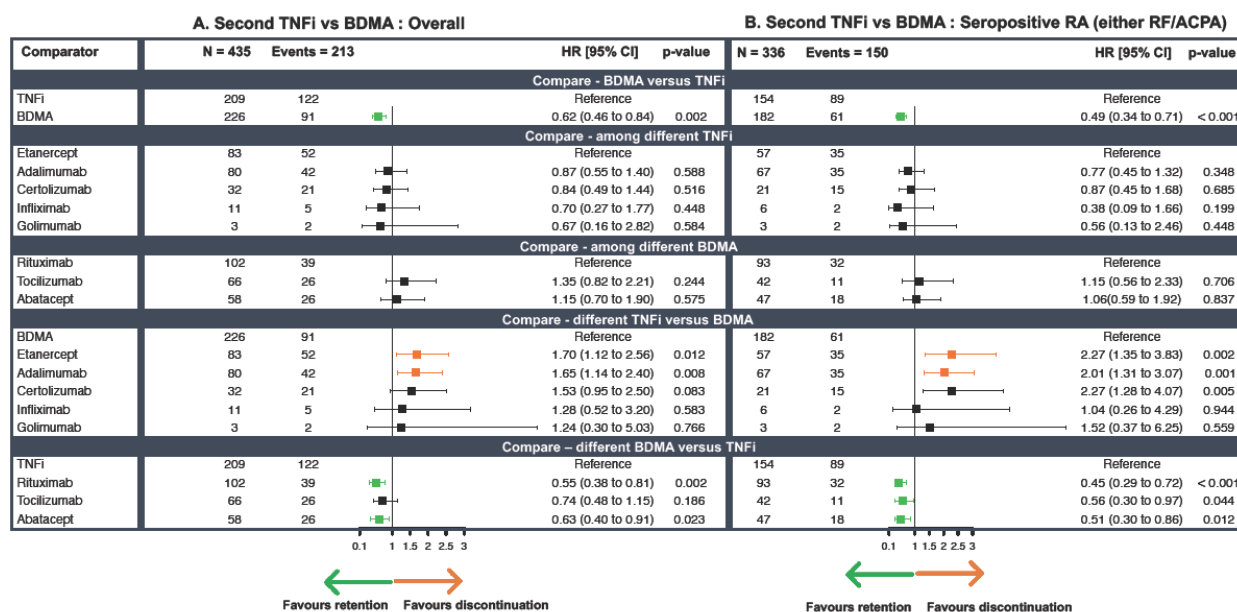


Figure 4 A-B: Survival-tree analysis of treatment-discontinuation of second-line therapy in rheumatoid arthritis (RA) patients, after discontinuation of the first-line TNFi (Tumour necrotic factor inhibitor) comparing second-line BDMA (Biologics of different mode of action) and TNFi. (A) Survival-tree with the terminal nodes. The initial tree was grown by binary splitting (splitting was based to minimise the Gini impurity) and then pruned back to terminal nodes. Kaplan-Meier (KM) survival curves of time to discontinuation of treatment among the terminal nodes are shown at the bottom of each node. (B) Hazard ratio (HR) [with 95%Confidence interval (CI)] of discontinuation of second-line biologics therapy among these terminal nodes.

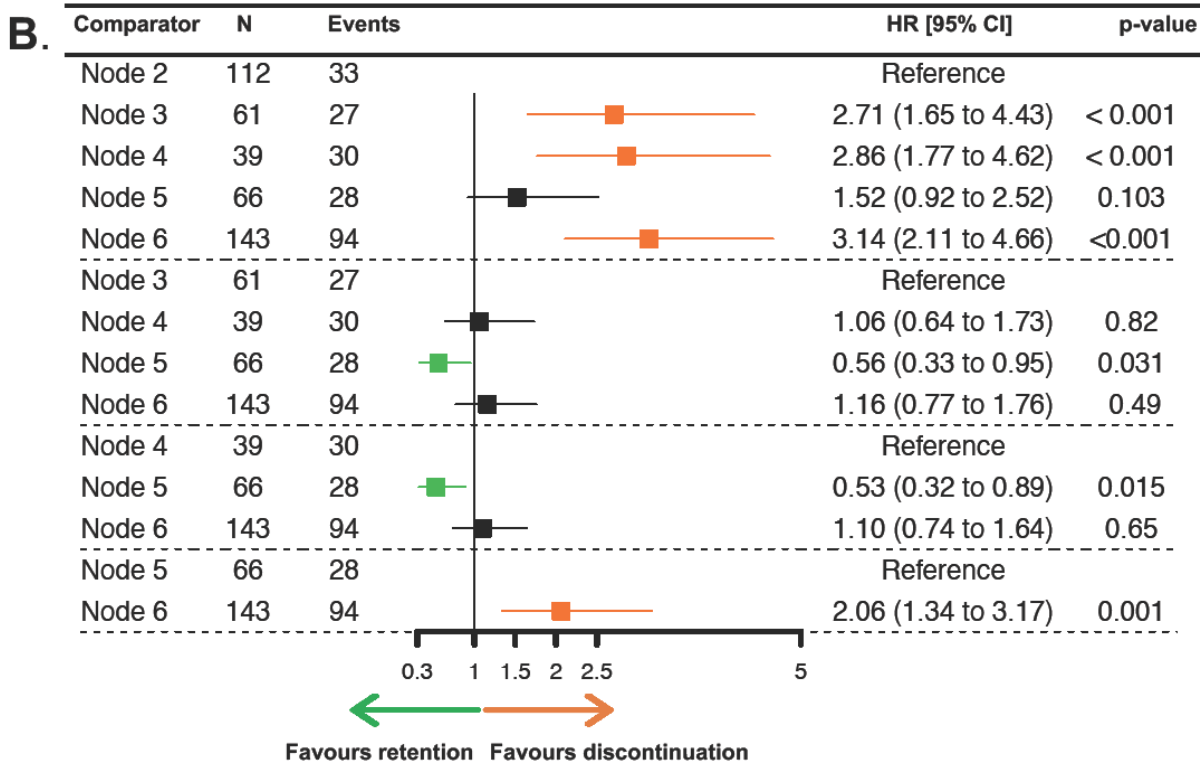
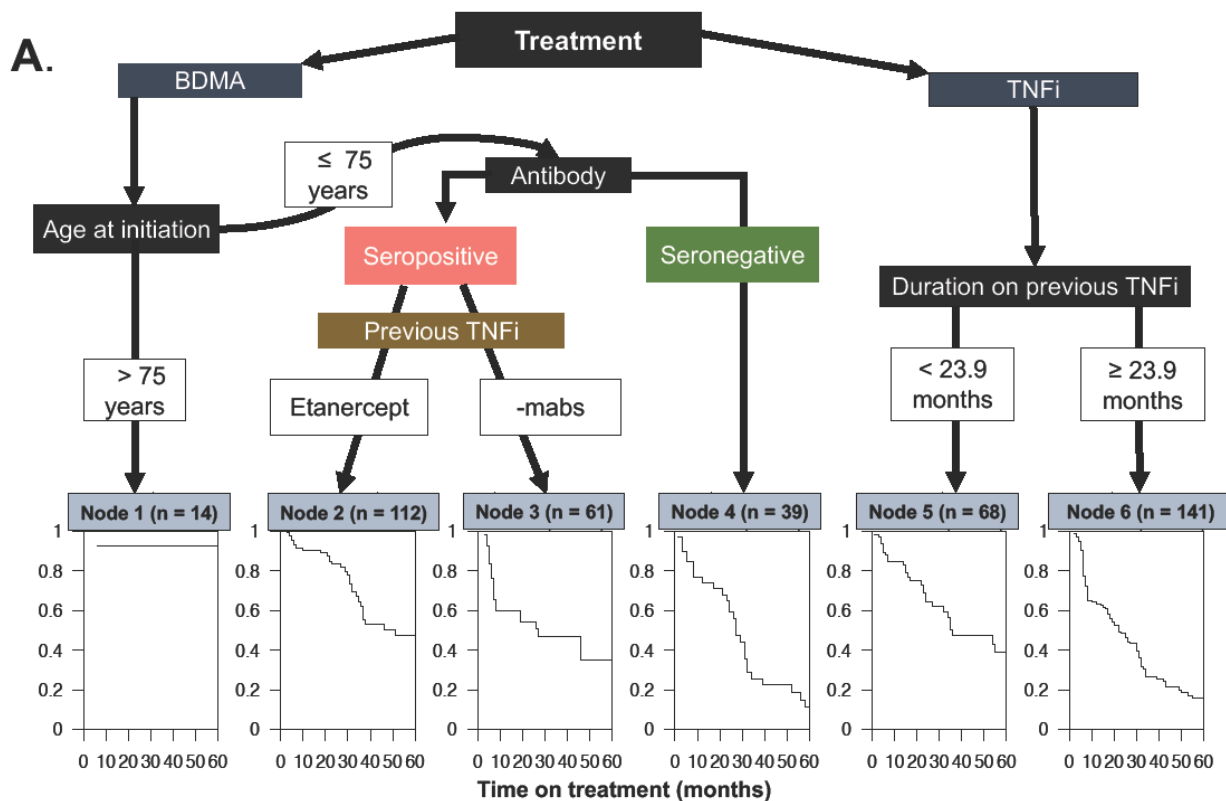


Figure 5 A-B: Comparison between second-line BDMA (Biologics of different mode of action) and TNFi (Tumour necrotic factor inhibitor). (A) Hazard ratio (HR) [with 95%Confidence interval (CI)] of discontinuation of second-line biologics therapy comparing BDMA versus TNFi, stratified by antibody status and type of previous TNFi (Etanercept/its biosimilars versus monoclonal-TNFi/-mabs = adalimumab/its biosimilars, infliximab, certolizumab, and golimumab), and adjusted by propensity quintile score[†]. (B) KM survival curve of time to treatment-discontinuation between TNFi and BDMA in patients who discontinued their first-line TNFi within 23.9months after initiation.

[†] Propensity quintile was adjusted for age of initiation of second biologics, disease duration at the initiation of second biologics, duration of first biologics, cause of discontinuation of first biologics, sex, baseline disease activity score (DAS28-ESR), c-reactive protein at baseline, tender and swollen joint count at baseline, patients' global VAS, Erythrocyte sedimentation rate (ESR) at baseline, concomitant use of conventional synthetic disease-modifying anti-rheumatic drugs.

ACCEPTED MANUSCRIPT

