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Towards Defining Primary and Secondary Non-Response in Rheumatoid Arthritis Patients Treated with Anti-TNFs: Results from the BioTRAC and OBRI Registries

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Short running head: 1ry/2ry Non-Response to Anti-TNF

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Abstract

**Background:** Although most RA patients respond to anti-TNF treatment, some present with initial (‘1ry’) non-response or lose initial responsiveness (‘2ry’ non-response). We compared the rate of real-world ‘non-response’ to first anti-TNF as reported by treating physicians to the non-response rate per accepted definitions and recommended treat-to-target strategies.

**Methods:** Patients from the BioTRAC and OBRI registries, on their first anti-TNF, with ≥1 follow-up visit were included. Post-hoc re-classification of physician-reported ‘non-response’ was based on prior achievement of DAS28-ESR low disease activity (LDA), CDAI LDA, or good/moderate EULAR response, and actual time of physician-reported ‘non-response’.

**Results:** Among 736 BioTRAC and 640 OBRI patients, 13.7% and 18%, discontinued their anti-TNF due to physician-reported ‘non-response’. Based on re-classification using disease activity, 65.6% (BioTRAC) and 87.2% (OBRI) of ‘1ry non-responders’ did not achieve DAS28-ESR LDA, 65.6%/90.7% CDAI LDA, and 46.9%/61.5% good/moderate EULAR response. Among ‘2ry non-responders’, 50.7%/47.8% did not achieve DAS28-ESR LDA, 37.7%/52.9% CDAI LDA, and 15.9%/19.6% good/moderate EULAR response before treatment discontinuation. Regarding actual time of ‘non-response’, 18.8% of BioTRAC and 60.8% of OBRI ‘1ry non-responders’ discontinued at ≤6 months. In both registries, a high proportion of ‘2ry non-responders’ discontinued their anti-TNF after 12 months (87.0% BioTRAC, 60.9% OBRI).

**Conclusion:** Physician-reported ‘1ry non-response’ was more correlated with non-achievement of DAS28-ESR LDA or CDAI LDA, whereas ‘2ry non-response’ with actual time of discontinuation. Further work is needed to confirm the importance of response and type of response to the initial anti-TNF in identifying patients most likely to benefit from a second biologic agent treatment.

**Keywords:** Tumor necrosis factor inhibitors, biological therapy, registries, physician practice patterns, rheumatoid arthritis
Introduction

Current rheumatoid arthritis (RA) treatment guidelines advocate the use of biological DMARDs (bDMARDs) for RA patients who have failed treatment with methotrexate (MTX) and/or other conventional synthetic DMARDs (csDMARDs), these patients being labelled as MTX/csDMARD incomplete responders (MTX/csDMARD-IR) (1). Nine biologics and 1 small molecule DMARD are currently available for use, which, in a recent Cochrane review, were found to improve prognosis by attenuating radiographic progression and conferring greater rates of treatment response and remission when used in MTX/csDMARD-IR patients (1).

Nevertheless, approximately one third of RA patients continue to fail to meet clinical endpoints of response on bDMARD/csDMARD combination therapy (2, 3). For these patients, successive biologic switching, either within the same, or to different mechanistic class(es), is advocated by all major international treatment guidelines (4-6). Patients not responding to biologic therapy may be categorized as primary (1ry) or secondary (2ry) non-responders, the former due to initial lack of response, and the latter due to loss of responsiveness over time (3).

Although current best-practice guidelines advocate the implementation of patient-centric treatment goals and treat to target strategies, the criteria for response differ across guidelines (4-6), potentially fragmenting the application of outcome measures into regionally specific preferences. Consequently, clinical studies employ definitions of treatment response that may differ in both the timing and criteria used (2, 7-16) limiting their comparability. Furthermore, recent data suggests that primary anti-TNF non-responders differ in their response to a second anti-TNF compared to 2ry non-responders (17-19); 1ry non-responders of the first anti-TNF are less likely to respond to a second anti-TNF while 2ry non-responders are more likely to respond to a second anti-TNF. These data have implications for the current
algorithm of care using anti-TNF therapy that suggests that prior primary failure of an anti-TNF should lead to use of biologic with a different mechanism of action.

Characterization of this heterogeneity in response definitions, and the associated implications, remains to be fully assessed in routine clinical practice settings. Using data derived from RA patients enrolled in the Biologic Treatment Registry Across Canada (BioTRAC) registry and the Ontario Best Practices Research Initiative (OBRI) clinical registry, two analyses were independently conducted to explore what treating rheumatologists considered ‘1ry or 2ry non-response’ of anti-TNF therapy in their routine clinical practice. To answer this question, we assessed the rate of ‘non-response’ based on the judgement of the treating physicians, among RA patients treated with their first anti-TNF in Canadian routine clinical practice and contrasted them to the rate of non-response using standard guideline definitions (4-6).

**Materials and Methods**

**Registry Descriptions**

In accordance with the observational nature of a registry, the management of patients enrolled in both the BioTRAC and OBRI registries, including the frequency of assessments, is based on the medical judgment of the treating physician, and all treatment(s) must be prescribed in accordance with the respective Canadian Product Monograph(s) (6, 20-23). All patients enrolled provided written informed consent, and approvals for participation were obtained from the local Research Ethics Boards of participating academic sites, and central Institutional Review Boards for non-academic sites (OBRI REB#: 07-0729 AE; BioTRAC REB: IRB Services, Ontario Canada). The BioTRAC and OBRI registries are conducted as per the tenets of the Declaration of Helsinki.

**BioTRAC Registry**

The BioTRAC Registry is an ongoing, Canada-wide, multi-center, observational, prospective study of patients initiating treatment with infliximab (IFX, REMICADE®, Janssen Inc., Toronto, Canada) or
golimumab (GLM, SIMPONI®, Janssen Inc., Toronto, Canada) for RA, ankylosing spondylitis (AS), or psoriatic arthritis (PsA), or with ustekinumab (UST, STELARA®, Janssen Inc., Toronto, Canada) for PsA. The goal of the registry is to collect real-world clinical, laboratory, patient-centric, and safety data in PsA, AS and RA patients treated in routine care (24). Patients ≥18 years old, who are biologic-naïve, or patients who have been previously treated with one biologic agent, are considered for inclusion in the registry. Patients are followed from initiation of IFX, GLM or UST, to treatment discontinuation. At the time of analysis, BioTRAC had collected data from over 80 rheumatology practices, with over 3,000 RA, AS, and PsA patients enrolled. In this study, only the RA patients were included.

**OBRI Registry**

The Ontario Best Practices Research Initiative (OBRI), founded in 2005, is a prospective registry of RA patients followed long-term in routine care in Ontario, Canada (25, 26). All patients ≥18 years of age, diagnosed with RA after the age of 16, and presenting with active disease (defined as at least 1 swollen joint) are eligible for inclusion (26). Registry goals include reporting on the safety, effectiveness and sustainability of available RA therapies, identifying clinical practice patterns for the improvement of patient outcomes, as well as using clinical and economic outcome data to inform health care policy (26). Over 2,500 patients were enrolled from over 60 rheumatology practices at the time of analysis (25, 27).

**Analysis Populations: Selection Criteria**

Biologic-naïve RA patients initiating their first anti-TNF agent, with available information on DAS28-ESR at baseline, and at least one post-baseline visit, were initially selected from both registries. Those discontinuing treatments due to ‘non-response’ as per the treating physician’s judgment were included in all analyses. Baseline was considered as the date of initiation of the first anti-TNF; for OBRI, a window of <30 days prior to enrolment in the registry was allowed for anti-TNF initiation, and baseline disease activity scores were assessed within 60 days before and 30 days after anti-TNF initiation.
Treatment Response

The BioTRAC and OBRI registries evaluate response to anti-TNF therapy based on the judgement of the treating physician. OBRI registry patients not responding to treatment per the judgment of the treating physician are categorized by the treating physician as ‘1ry non-response’ (failure to achieve initial response), or as loss of response (failure to maintain response after a recommended period of ≥3 months). BioTRAC patients discontinuing anti-TNF treatment due to effectiveness reasons, are classified by the treating physician as experiencing either a lack of response (‘1ry non-response’), loss of response (‘2ry non-response’).

Post-hoc re-classifications of physician-reported ‘non-response’ to the first anti-TNF agent were performed by the authors for both registry analyses. One re-classification was based on whether a patient clinically responded to treatment, i.e. whether (i) a Disease Activity Score (DAS) of ≤ 3.2 (low disease activity - LDA), (ii) good/moderate EULAR response, or (iii) a Clinical Disease Activity Index (CDAI) score of ≤ 10 (LDA), was achieved (28). A second re-classification was based on actual time of physician-reported ‘non-response’, categorized as ≤6, >6-≤12, or >12 months.

Statistical Analysis

BioTRAC and OBRI

Descriptive statistics were produced for all baseline patient, disease, and treatment characteristics, which included the mean and standard deviation for continuous variables, and proportions for categorical variables.

The agreement between physician-reported ‘non-response’ and re-classification categories was assessed descriptively with the concordant pairs. Time to discontinuation of the first anti-TNF treatment regimen was also assessed with the Kaplan Meier (K-M) estimate of the survival function.
Statistical analyses were carried out using SPSS 24.0 (SPSS Inc., Chicago, IL) and SAS 9.2 (SAS Institute, Cary, NC).

Results

Patient disposition and baseline characteristics

Overall, 736 BioTRAC and 640 OBRI patients met the selection criteria (Figure 1), of which 480 (65.2%) and 242 (37.8%), respectively, discontinued their first anti-TNF treatment due to any reason after 2632 and 1114 person-years of follow-up. Median (95% CI) K-M based time to discontinuation was 3.4 (2.9-4.0) years and 3.6 (3.0-4.8) years in BioTRAC and OBRI, respectively; 1-year and 5-year survival probabilities were 85.5% and 42% in BioTRAC, and 74.2% and 43% in OBRI. Discontinuation due to physician-reported anti-TNF ‘non-response’ was reported for 101 (13.7%) and 115 (18%) of patients in BioTRAC and OBRI, respectively, which comprised the analysis populations. Within anti-TNF ‘non-responders’ as per the physicians’ judgment, the rate of ‘1ry non-response’ was 31.7% (n=32) in BioTRAC and 44.3% (n=51) in OBRI, the remaining 68.3% (n=69) and 55.7% (n=64), respectively, judged as ‘2ry non-responders’.

Table 1 provides a summary of the baseline patient and disease characteristics for the two analysis populations of RA. In addition, the characteristics of the overall registries of RA patients are provided for assessment of the comparability of each analysis population with the total population within the respective registry. At anti-TNF initiation, patients in the BioTRAC registry were more likely to be anti–citrullinated protein antibody (ACPA) positive (41.2% vs. 34.2%) and had higher disease activity as indicated by the higher DAS28-ESR score (5.6 vs 5.2), swollen (9.5 vs. 7.2) and tender (11.2 vs. 8.4) joint counts, and patient global assessment (6.3 vs. 5.7). Both analysis populations were generally comparable to their respective total cohorts except for disease duration at baseline and follow-up duration which were shorter in the analysis populations.
Re-classification of physician-reported ‘non-response’ to first anti-TNF

Reclassification based on disease activity

Physician-reported patient’s ‘non-response’ (1ry or 2ry) was contrasted to reclassification based on response criteria, specifically the achievement of DAS28 LDA, CDAI LDA, and good/moderate EULAR response prior to treatment discontinuation. Importantly, 65.6% of BioTRAC and 87.2% of OBRI physician-reported ‘1ry non-responders’ did not achieve DAS28-ESR LDA (Figure 2A), 65.6% and 90.7%, respectively, did not achieve CDAI LDA (Figure 2C), and 46.9% and 61.5%, respectively, did not achieve good/moderate EULAR response (Figure 2E).

Among physician-reported ‘2ry non-responders’ in both registries almost half of patients did not achieve LDA prior to treatment discontinuation (50.7% BioTRAC and 47.8% in OBRI) (Figure 2B), 37.7% and 52.9%, respectively, did not achieve CDAI LDA (Figure 2D), and 15.9% and 19.6% did not achieve good/moderate EULAR response (Figure 2F).

Reclassification based on time of physician-reported ‘non-response’

Regarding actual time to physician-reported ‘non-response’, in the BioTRAC cohort, 18.8% of ‘1ry non-responders’ discontinued their first anti-TNF treatment prior to month 6, 40.6% discontinued >6-≤12 months, and 40.6% >12 months post anti-TNF initiation. In the OBRI cohort, 60.8% of 1ry non-responders discontinued treatment before 6 months, 25.5% between 6-12 months and 13.7% after 12 months respectively (Figure 3a).

Among patients judged by their treating physician as ‘2ry non-responders’, in the BioTRAC cohort, 1.4% discontinued treatment before 6 months, 11.6% between 6-12 months and 87.0% after 12 months of anti-TNF-initiation. In the OBRI cohort, 7.8% discontinued treatment before 6 months, 31.3% between 6-12 months and 60.9% after 12 months of anti-TNF-initiation. (Figure 3b).
Discussion

In this joint-registry analysis, discontinuation of a first anti-TNF regimen, for any reason, was reported by 65.2% and 37.2% of BioTRAC and OBRI patients, respectively, the difference most likely reflecting the longer overall follow-up of BioTRAC patients as well as differences in clinical practice between Ontario and other provinces (only covered in BioTRAC). Overall, these results are in agreement with a recent meta-analysis (29), reporting a rate of anti-TNF discontinuation for any reason at years 2, 3 and 4 of 37%, 44%, and 52%, respectively, as well as with other studies (30-34). However, discontinuations specifically for physician-reported ‘non-response’ in both registries were lower compared to the studies by Bartelds et al (25%) (34) and Hyrich et al (55%) (2).

Overall, physician-reported ‘1ry non-response’ was more correlated to non-achievement of DAS28-ESR LDA and non-achievement of CDAI LDA, rather than good/moderate EULAR response. Physician-reported ‘2ry non-response’ was more correlated with post-hoc reclassification based on actual time of discontinuation, rather than prior achievement of DAS28-ESR LDA, CDAI LDA, or good/moderate EULAR response. These results may reflect the heterogeneity of clinical parameters used to gauge response, in addition to patient and physician preferences that may drive retention of treatment, or conversely, cessation of treatment, regardless of treatment outcome (35, 36).

These results also suggest regional-specific patterns of RA management and could be taken as indication of the lack of consensus among physicians not only on the definition of treatment non-response, but also when a patient should be considered a 1ry non-response. As intensive, treat-to-target management of RA is advocated by Canadian and international treatment guidelines (4-6, 37), the observed delay with respect to 1ry non-response assessment also suggests that routine care may not completely align with current treatment paradigms; however, both registries included patients from both the pre- and post-
establishment of treat-to-target guidelines era which could also contribute in the heterogeneity in the definition of 1ry non-response.

It is important to emphasize to community physicians which criteria they should consider for definition of 1ry and 2ry ‘non-response’ to the first anti-TNF which might be able to be extrapolated to possibly predict response to the second anti-TNF. The findings of this study suggest that ‘1ry non-response’ definition should be based on non-achievement of DAS28-ESR LDA or CDAI LDA, whereas actual time of discontinuation should be used for defining ‘2ry non-response’.

The main limitation of our study is that the exact reasons for the physicians classifying a patient as a ‘1ry or 2ry non-responder’ were not available in either registry which would have allowed obtaining a more complete picture of clinical practise patterns and decision-making. An important strength of our study is the attainment of similar results in both registries which supports the reliability of the findings.

In summary, the results of this joint-registry analysis highlight physician-reported ‘1ry non-response’ was more correlated to non-achievement of DAS28-ESR LDA or CDAI LDA, whereas physician-reported ‘2ry non-response’ was more correlated with post-hoc reclassification based on actual time of discontinuation. Further work is needed to confirm the importance of 1ry and 2ry ‘non-response’ as well as the type of clinical response to the initial anti-TNF in identifying patients who are most likely to benefit from a second biologic agent treatment.
Acknowledgements

The authors wish to acknowledge the BioTRAC-RA and OBRI-RA investigators. The authors also wish to acknowledge JSS Medical Research for medical writing and editorial services.
References


**Figure Titles:**

Figure 1. Patient disposition

Figure 2. Proportions of patients achieving DAS28-ESR LDA, CDAI LDA, and good/moderate EULAR response by type of physician-reported ‘non-response’

Figure 3. Actual time of physician-reported ‘non-response’ by type of physician-reported ‘non-response’

**Figure Legends:**

Figure 1.
*Analysis population*
Table 1. Baseline RA patient demographic and disease characteristics by registry

<table>
<thead>
<tr>
<th></th>
<th>BioTRAC</th>
<th>OBRI</th>
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<tr>
<td></td>
<td>Overall</td>
<td>Anti-TNF Non-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Responders*</td>
</tr>
<tr>
<td>N (%)</td>
<td>736 (100.0)</td>
<td>101 (13.7)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>N=684</td>
<td>N=96</td>
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<tr>
<td></td>
<td>56.3 (13.3)</td>
<td>52.5 (13.5)</td>
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<td>Disease duration, years,</td>
<td>N=314</td>
<td>N=56</td>
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<tr>
<td>mean (SD)</td>
<td>8.7 (9.0)</td>
<td>7.4 (8.3)</td>
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<td>20.8 (20.3)</td>
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<tr>
<td>months, mean (SD)</td>
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<td>535 (75.8)†</td>
<td>76 (78.4)†</td>
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<td>ACPA positive, n (%)</td>
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<td>46 (53.5)</td>
<td>7 (41.2)</td>
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<td>DAS28-ESR, mean (SD)</td>
<td>N=736</td>
<td>N=101</td>
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<td></td>
<td>5.8 (1.8)</td>
<td>5.6 (1.4)</td>
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<td>N=736</td>
<td>N=101</td>
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<td></td>
<td>10.5 (7.0)</td>
<td>9.5 (6.8)</td>
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<td>TJC28, mean (SD)</td>
<td>N=736</td>
<td>N=101</td>
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<td>12.2 (7.9)</td>
<td>11.2 (7.3)</td>
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<td>PtGA, 0-10, mean (SD)</td>
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<td>6.0 (2.5)</td>
<td>6.3 (2.4)</td>
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<td>MDGA, 0-10, mean (SD)†</td>
<td>N=733</td>
<td>N=100</td>
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<tr>
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</tr>
<tr>
<td></td>
<td>6.4 (2.2)</td>
<td>6.7 (2.0)</td>
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<tr>
<td>Anti-TNF agent, n (%)</td>
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<tr>
<td>Etanercept</td>
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<td>Adalimumab</td>
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<tr>
<td>Infliximab</td>
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<td>77 (76.2)</td>
</tr>
<tr>
<td>Certolizumab</td>
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</tbody>
</table>

*Defined as physician-reported 1ry and 2ry non-responders.

† Proportions based on overall patients in the respective registry.

‡ Proportions based on total number of patients with available data.

BioTRAC
Initiated 1st anti-TNF
N=736

Discontinued (Any Reason)
N=480

Other
N=237

Adverse Event
N=91

Disease Progression
N=51

Not Discontinued
N=256

Non-Response*
N=101

1ry Non-Response
N=32

2ry Non-Response
N=69
Figure 2. Proportions of patients achieving DAS28-ESR LDA, CDAI LDA, and good/moderate EULAR response by type of physician-reported ‘non-response’
Figure 3. Actual time of physician-reported ‘non-response’ by type of physician-reported ‘non-response’

112x136mm (300 x 300 DPI)