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Reasons for b/tsDMARD cessation and persistence of second line treatment in a large real world rheumatoid arthritis dataset

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ABSTRACT

Objectives: To provide real world evidence about the reasons why Australian rheumatologists cease biologic (b) and targeted synthetic (ts) disease-modifying anti-rheumatic drugs (DMARDs) when treating rheumatoid arthritis (RA) patients and to assess primary failure rate for first-line treatment and the persistence on second-line treatments in patients who stopped first-line tumor necrosis factor inhibitors (TNFi).

Methods: This is a multi-centre retrospective, non-interventional study of RA patients enrolled in the Australian Optimising Patient outcome in Australian RheumatoLogy (OPAL) dataset with a start date of b/tsDMARDs between 1 August 2010 and 30 June 2017. Primary failure was defined as stopping treatment within 6 months of treatment initiation.

Results: Data from 7740 patients were analysed; 6914 patients received first-line b/tsDMARDs. First-line treatment was stopped in 3383(49%) patients; 1263(37%) were classified primary failures. The most common reason was "lack of efficacy" (947/2656; 36%). Of the patients who stopped first-line TNFi, 43% (1111/2560 patients) received second line TNFi, which resulted in the shortest median time to stopping second-line treatment (11 months, 95% CI 9-12) compared with non-TNFi. The longest second-line median treatment duration after first line TNFi was for patients receiving rituximab (39 months; 95% CI 27-74).

Conclusion: A large proportion of patients who stopped first-line TNFi therapy received another TNFi despite evidence for longer treatment persistence on second-line b/tsDMARDs with a different mode of action. Lack of efficacy was recorded as the most common reason for making a switch in first-line treatment of RA patients.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic progressive systemic autoimmune disease that results in significant pain, progressive joint damage, functional disability, and impaired quality of life (1, 2). There are eight bDMARDs, more than twelve cDMARDs, and two targeted synthetic DMARDs (tsDMARD) approved for the treatment of RA in Australia. Comparisons between available drugs in head-to-head randomized controlled trials (RCTs) are rare (3, 4) and current guidelines recommend that patients can be started on any one bDMARD as first and second line treatment (5, 6). As a result, treatment choices can be difficult.

A number of factors may influence treatment choices in the real world practice setting. Although there have been various studies investigating treatment choices and the effectiveness of these treatments using data derived from several patient registries (7-10), the reasons why individual b/tsDMARDs are discontinued have not been well documented.

Some patients are refractory to b/tsDMARD and experience primary failure to treatment while others show initial clinical response but eventually lose responsiveness (secondary failure). The primary failure rate for b/ts DMARDs is currently unknown in Australia.

Persistence on treatment has been suggested as a surrogate for treatment effectiveness and the persistence of bDMARDs in Australian RA patients has been investigated (7, 11). However, to our knowledge, no study has included all of the currently available b/tsDMARDs modes of action when investigating second line persistence after first line Tumor Necrosis Factor inhibitors (TNFi) therapy.

This study aimed to use the Optimizing Patient outcome in Australian RheumatoLogy (OPAL) dataset to provide real world evidence about the reasons behind stopping b/tsDMARD treatment in the Australian RA population. The study also aimed to provide real world evidence on the effectiveness of b/tsDMARDs in the first and second line setting through assessment of the first line primary failure rate and persistence of second line

treatment after first line TNFi failure. The study focused on persistence after first line TNFi failure since TNFis are the most commonly prescribed first line bDMARDs for the treatment of RA in Australia.

PATIENTS AND METHODS

Study Design and Objectives

This is a multi-centre retrospective, non-interventional study of RA patients treated in Australia, in routine clinical practice. The objectives of the study were to identify the reasons why Australian rheumatologists are ceasing b/tsDMARDs for the treatment of RA, to assess primary failure rate for first line b/tsDMARD treatment and to identify treatment choices after cessation of first line TNFi and the persistence of the second line treatments.

First line treatment refers to patients who received b/tsDMARD treatment for the first time. Second line treatment refers to patients who received their second b/tsDMARD treatment. Primary failure was defined as stopping treatment within 6 months. In the absence of disease activity data, the 6-month cut-off was chosen based on the local re-imbursement requirements for demonstration of response to treatment within 12-16 weeks of starting a b/tsDMARDs; Australian clinicians are required to provided documentations of adequate response to treatment, in order for the patient to continue to receive reimbursed supply of treatment (12). Under the Australian Pharmaceutical Benefit Scheme (PBS), when a patient is commenced on any of the available b/ts DMARD, the treating clinician must document in a written application, a 20% reduction in ESR or CRP and a 50% reduction in active joint count after 12 weeks for approval for continuing treatment. Following the approval of the first repeat prescription, the reduction in active joint count and ESR or CRP must be maintained and documented every 6 months in subsequent applications for approval of repeat prescriptions. Therefore, secondary failure was defined as stopping treatment any time after 6 months of treatment initiation.

Data Capture

De-identified data were extracted from the Australian OPAL dataset from 37 rheumatology practices. The OPAL dataset collects information from individual physicians' servers entered during routine clinical consultations, using purpose-built worksheets in Audit4 software (Software4Specialists, Australia). This software serves as the patient's medical record. Physicians can choose reasons for treatment cessation from a pre-specific list of options (Supplementary Table 1). The reason for cessation of a b/tsDMARD is a mandatory field when a treatment stop date is recorded and only one reason can be chosen for a given treatment.

The activities of OPAL Rheumatology Ltd. have received overarching ethics approval from the University of New South Wales Human Research Ethics Committee based on a patient opt out arrangement. This research protocol was approved by the University of New South Wales Human Research Ethics Committee (HC17232).

Patient Population and Eligibility Criteria

Patients were included if they were registered in the OPAL dataset, were at least 18 years of age and started a b/tsDMARD for the treatment of their RA between 1 August 2010 and 30 June 2017. The 1st of August 2010 date was chosen as it was the date from which all bDMARDs, under consideration in this study, were reimbursed through the Australian PBS (12).

Patients were excluded if they or their physicians opted out of data collection.

Statistical and Analytical Assessment

Data were analysed using SAS (Proprietary Software) V 9.4. There were instances where the stop dates for a b/tsDMARD were missing. For these cases the stop dates were imputed. For example, if the stop date of a b/tsDMARD was missing (and there was a subsequent b/tsDMARD listed), the stop date was imputed as the day before the next b/tsDMARD start

date. There were 546 (8%) instances of this (where the stop date for the b/tsDMARD was missing) and the imputation was as described – i.e. the stop date for the first b/tsDMARD was set to the day before the start date of the following b/tsDMARD. In addition, there were 425 (6%) instances where the stop date for the b/tsDMARD was after the start date of the next b/tsDMARD. Therefore, the stop date for the first b/tsDMARD was set to the day before the start date of the following b/tsDMARD. Treatment persistence was defined as the duration of time between initiation and cessation of treatment. If there was no medication end date and no other medication initiated, it was assumed that the medication was ongoing (censored) at the time of data extraction (30 June 2017). Comparisons between treatment persistence by treatment type were done using Kaplan-Meier methodology. The persistence results for individual TNFi therapies were grouped together as there is evidence that the persistence is similar between the different TNFi therapies in Australia (7, 11).

Descriptive statistics (mean, median, range and 95% confidence intervals) are provided for continuous variables and frequency counts and 95% confidence intervals for categorical variables. The frequency and type of reasons given to justify cessation of b/tsDMARD medication were summarised and reported.

At the time of data extraction, nine b/tsDMARDs were approved in Australia including the TNFi adalimumab (subcutaneous (SC)), etanercept (SC), golimumab (SC), certolizumab pegol (SC), and infliximab (intravenous (IV)). Other b/tsDMARDs investigated were tocilizumab (SC and IV), abatacept (SC and IV), rituximab (IV), and tofacitinib (oral, tsDMARD).

RESULTS

Patients and treatments

There were 25,237 RA patients in the OPAL dataset (Figure 1). Of the 7,740 who started a b/tsDMARD for the treatment of their RA between 1 August 2010 and 30 June 2017, 6914

patients received first line b/tsDMARD treatment. The majority were female (n= 5186; 75%) with a median age of 61 years (18 to 96 years) and a median disease duration (onset to last visit) of 10 years (0 to 73 years) (Table 1).

Etanercept was the most commonly prescribed first line agent (n= 1868; 27%), followed by adalimumab (n= 1788; 26%), golimumab (n= 832; 12%), abatacept (n= 609; 9%), tocilizumab (n= 555; 8%), tofacitinib (n= 518; 7.5%), certolizumab pegol (n= 457; 7%), rituximab (n= 230; 3%) and infliximab (n= 57; 1%; Table 1).

First-line treatment was stopped in 3383 (49%) patients of whom 1263 (37%) experienced a primary failure as assessed by our definition (Table 2). In patients who stopped treatment, the highest percentage of primary failure was for patients receiving tofacitinib (124/185, 67%) and the lowest percentage of primary failure was for patients receiving tocilizumab (57/288, 20%).

A total of 5002 patients received first-line TNFi; 2560 (51%) patients stopped first line treatment of whom 964 (38%) and 1596 (62%) were classified as primary failures and secondary failures respectively.

Physician Reported Reasons for Treatment Cessation

There were 2656 reasons for cessation recorded by the treating physician for the 3383 patients who stopped first-line b/tsDMARDs and 928 reasons for the 1263 patients who were classified as primary failures of first line b/tsDMARDs (Table 3).

For all patients who stopped first-line b/tsDMARDs, the most common reason for cessation was recorded as “lack of efficacy" (947/2656, 36%). Certolizumab pegol had the highest (114/221, 52%) and infliximab had the lowest (4/25, 17%) proportion of treatment cessation recorded as “lack of efficacy”. Tofacitinib had the highest proportion (22/105, 21%) and golimumab had the lowest proportion (22/327, 7%) of discontinuations due to “adverse reactions”.

In the subset of patients classified as primary failures, the most common reason for treatment cessation was recorded as "lack of efficacy" (233/928, 25%). Certolizumab pegol (60/92, 65%) had the highest proportion and rituximab had the lowest (1/11, 9%) proportion of discontinuation due to "lack of efficacy". Infliximab (2/6, 33%) had the highest proportion and golimumab (12/139, 7%) the lowest proportion of discontinuation due to "adverse events".

Persistence on b/tsDMARDs post first-line TNF inhibitors

Persistence on second-line b/tsDMARDs was assessed for patients who stopped first-line TNFi only, considering the low number of patients on other b/tsDMARDs.

Of the patients who stopped first-line TNFi, 43% (1111/2560 patients) received second-line TNFi and this resulted in the shortest median time to stopping second line treatment (11 months; 95% CI:9-12) (Figure 2). The longest second-line median treatment duration after first line TNFi was for patients receiving rituximab (39 months; 95% CI: 27-74).

Of the 964 patients classified as having a primary failure to first line TNFi, 322 patients had a physician recorded "lack of efficacy" as the reason for treatment cessation of whom 309 (96%) received second line treatment. The majority received other TNFi (n=130, 42%) (Table 4). The persistence rate on second line b/tsDMARD treatment (Table 4) was highest for tocilizumab (78%) at 6 months and rituximab (75%) at 12 months and lowest for TNFi (60% at 6 months and 40% at 12 months). The median time to stopping second line treatment was the longest for rituximab (49 months; 95% CI:17-74) and shortest for TNFi (9 months; 95% CI:7-12) (Table 4).

Of the 1596 patients classified as secondary failures to the first-line TNFi, 429 patients had "lack of efficacy" recorded as reason for cessation by the treating physician. The majority of these patients received other TNFi (n=200, 47%) as second-line treatment (Table 4). The second-line persistence rates in this group were highest for rituximab at both 6 and 12 months (83% and 69%, respectively) and lowest for tofacitinib (58% at 6 months and 29% at 12

months); it is important to keep in mind that the data is not mature enough for persistence on tofacitinib, considering it became available on the PBS from October 2015. The median time to stopping second line treatment was the longest for rituximab (39 months; 95% CI: 9-ND) and shortest for TNFi (11 months; 95% CI: 9-15) (Table 4).

DISCUSSION

Data from controlled clinical trials suggest that approximately one third of RA patients experience primary response failure to a TNFi (13-15) and a significant proportion of patients will also experience a secondary failure after an initial response (16). One might expect that patients with a primary failure to a TNFi would be less likely to respond to a second TNFi than those who have sustained a secondary failure. This question has not been previously addressed in a large cohort of patients and particularly not in a real world evaluation. Our study used the Australian OPAL dataset, which is one of the largest clinical practice datasets in the world, to determine the reasons for cessation of first-line treatment with b/tsDMARDs in patients with RA and also whether the effectiveness of second-line TNFi was dependent on whether the failure to first-line TNFi was primary or secondary.

The most common reason for b/tsDMARDs treatment cessation was recorded by the treating physician as "lack of efficacy" which is consistent with findings from a number of registries as well as other retrospective observational studies (10, 17-20).

The rate of first-line treatment discontinuation in our study is slightly higher (49%) than that reported in a Canadian (38%) and United Kingdom (45%) study (21, 22). The overall primary failure rate for all b/tsDMARDs as defined by cessation of treatment within 6 months was 37%, with a large variation observed across the individual b/tsDMARDs. Of interest is the high primary failure rate observed for patients treated with tofacitinib (67%).

To our knowledge this is the first study that has investigated the primary failure rate of tofacitinib in real world setting.

A large number of patients (43%) received a second line TNFi after stopping first line TNFi which resulted in the lowest median treatment persistence compared to second line b/tsDMARDs with a different mode of action. This is consistent with results from other studies demonstrating that patients who switched to another TNFi after first line TNFi failure had an inferior persistence compared to those who switched to non TNFi treatment (20, 23-25).

Our results have also shown that the persistence on a second-line TNFi was lower than on bDMARDs with a different mode of action, regardless of whether the patients experienced primary or secondary failure to the first-line TNFi due to "lack of efficacy". Furthermore, primary or secondary failure of the first line TNFi does not appear to affect the physician's decision to prescribe a second TNFi, with the proportion of patients receiving a second TNFi being similar in both groups.

Patients receiving second line rituximab and tocilizumab after failure of TNFi had higher persistence rates and longer median treatment duration compared to other b/tsDMARDs. This is in agreement with current literature (24-27). Other observational studies reported that patients who had failed one TNFi demonstrated better disease activity when switched to rituximab compared to switching to an alternative TNFi (28-30).

It is important to acknowledge the limitations of our study, being a retrospective study with some missing data points has resulted in assumptions being made in some cases regarding treatment start and stop dates. This study is also limited by the Lack of specific clinical disease activity measures and was unable to document the magnitude of response for each of the drugs under study. However, built into the Australian PBS approval for continuing treatment is a documentation of clinical response, whereby persistence on drug requires the treating clinician to document a reduction in inflammatory markers and a reduction in active

joint counts which is an indicator of persistent clinical response. Also, given the type of data available in this dataset, we did not attempt to match underlying disease conditions across treatment groups; and therefore treatment choices may reflect other clinical characteristics that were not accounted for in this analysis. However, the large number of patients studied reduces the likelihood that differences in the baseline clinical characteristics in the treatment groups altered the outcomes. Results for sub-groups with small number of patients, particularly for infliximab and rituximab, should be interpreted with caution.

In conclusion, this large real world study found that "lack of efficacy" as classified by the treating physician was the most common reason for cessation of the first-line b/tsDMARDs. Switching to a second TNFi after discontinuation of first line TNFi therapy resulted in the lowest treatment persistence when compared to switching to b/tsDMARDs with other modes of action. Nevertheless, a large proportion of the patients who stopped first-line TNFi therapy were started on another treatment with the same mode of action.

AUTHOR CONTRIBUTIONS

PY and GL are the principal investigators on the study and were involved in study design, protocol development, data acquisition and interpretation of results, and preparation of the manuscript. BM was the clinical scientist on the study and was involved in study design, protocol development, data acquisition and interpretation of results, and preparation of the manuscript. PB and MT were the statisticians on the study and were involved in study design, protocol development, data acquisition and interpretation of results, and preparation of the manuscript. HG, Paul Bird, LR and KT are members of the OPAL Steering Committee and were involved in the study design, data acquisition and interpretation of the results, and the development of the manuscript. All authors reviewed and approved the final manuscript.

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Figure Legends

Figure 1: Flow diagram of rheumatoid arthritis patients in the OPAL dataset included in the study.

Figure 2: Kaplan-Meier plot of second line persistence post discontinuation of first line TNF inhibitors regardless of reason for cessation.

Table 1 Demographics and baseline characteristics for patient on first line b/tsDMARD treatment

Factor	All N= 6914[b]	Rituximab N= 230 [b]	Tocilizumab N= 555 [b]	Tofacitinib N= 518 [b]	Abatacept N= 609 [b]	TNFi N= 5002[b]	Adalimumab N= 1788 [b]	Certolizumab pegol N= 457 [b]	Etanercept N= 1868 [b]	Golimumab N= 832 [b]	Infliximab N= 57 [b]
Age (years)	**n= 6911**	**n= 230**	**n= 555**	**n= 518**	**n= 609**	**n= 4999**	**n= 1786**	**n= 457**	**n= 1868**	**n= 831**	**n= 57**
Median (min:max)	61 (18:96)	68 (34:89)	62 (19:93)	62 (18:95)	64 (24:96)	60 (18:96)	59 (18:93)	60 (20:95)	61 (19:96)	61 (19:91)	60 (26:85)
Gender, n (%)	**n= 6914**	**n= 230**	**n= 555**	**n= 518**	**n= 609**	**n= 5002**	**n= 1788**	**n= 457**	**n= 1868**	**n= 832**	**n= 57**
Female	5186 (75)	153 (67)	424 (76)	384 (74)	469 (77)	3756 (75)	1342 (75)	342 (75)	1401 (75)	629 (75)	42 (74)
Male	1678 (24)	76 (33)	128 (23)	134 (26)	130 (21)	1210 (24)	432 (24)	112 (24)	452 (24)	200 (24)	14 (25)
Unassigned	50 (1)	1 (0)	3 (1)	-	10 (2)	36 (1)	14 (1)	3 (1)	15 (1)	3 (1)	1 (1)
RA duration[a] (years)	**n= 4112**	**n= 122**	**n= 295**	**n= 321**	**n= 308**	**n= 3066**	**n= 1061**	**n= 323**	**n= 1127**	**n= 529**	**n= 26**
Median (min:max)	10 (0:73)	17 (1:54)n	10 (0:73)	6 (1:61)	12 (1:57)	10 (0:67)	10 (0:67)	9 (0:47)	10 (0:61)	9 (1:67)	16 (1:41)
CCP category, n (%)	**n= 2087**	**n= 54**	**n= 133**	**n= 147**	**n= 188**	**n= 1565**	**n= 510**	**n= 114**	**n= 683**	**n= 253**	**n= 5**
≤ 5	1049 (50)	23 (43)	78 (59)	81 (55)	89 (47)	778 (50)	300 (59)	57 (50)	306 (45)	111 (44)	4 (80)
> 5	1038 (50)	31 (57)	55 (41)	66 (45)	99 (53)	787 (50)	210 (41)	57 (50)	377(55)	143 (56)	1 (20)
RhF category, n (%)	**n= 3470**	**n= 91**	**n= 234**	**n= 272**	**n= 332**	**n= 2541**	**n= 846**	**n= 229**	**n= 1024**	**n= 423**	**n= 19**
≤ 14	1369 (39)	30 (33)	99 (42)	117 (43)	122 (37)	1001 (39)	388 (46)	82 (36)	348 (34)	173(41)	10 (53)
> 14	2101 (61)	61 (67)	135 (58)	155 (57)	210 (63)	1540 (61)	458 (54)	147 (64)	675 (55)	250(59)	9 (47)

CRP, n	**n= 6772**	**n= 219**	**n= 537**	**n= 511**	**n= 600**	**n= 4905**	**n= 1749**	**n= 447**	**n= 1832**	**n= 823**	**n= 54**
Median (min:max)	5 (0:455)	5 (0:225)	5 (0:316)	5 (0:217)	5 (0 170)	5 (0:455)	5 (0:247)	5 (0:406)	5 (0:283)	5 (0:216)	5 (0:455)
ESR, n	**n= 6770**	**n= 218**	**n= 537**	**n= 511**	**n= 599**	**n= 4905**	**n= 1747**	**n= 448**	**n= 1834**	**n= 823**	**n= 53**
Median (min:max)	13 (0:140)	14 (1:115)	14 (1:129)	12 (1:136)	14 (1:118)	13 (0:14)	13 (1:134)	14 (1:116)	13 (1:140)	14 (0:130)	9 (1:135)
Smoking status, n(%)	**n= 6914**	**n= 230**	**n= 555**	**n= 518**	**n= 609**	**n= 5002**	**n= 1788**	**n= 457**	**n= 1868**	**n= 832**	**n= 57**
Current	143 (2)	7 (3)	20 (4)	10 (2)	11 (2)	95 (2)	30 (2)	6 (1)	45 (2)	13(2)	1(2)
Former	369 (5)	16 (7)	12 (2)	26 (5)	40 (7)	275 (6)	92 (5)	26(6)	119 (7)	37(4)	1(2)
Never	533 (8)	13 (6)	37 (7)	39 (8)	44 (7)	400 (8)	138 (8)	30(7)	154 (8)	74(9)	4(7)
Unknown	5869 (85)	194 (84)	486 (88)	443 (86)	514 (84)	4232 (85)	1528 (85)	395 (86)	1550 (83)	708(85)	51(89)
Steroid use, n(%)	**n= 6914**	**n= 230**	**n= 555**	**n= 518**	**n= 609**	**n= 5002**	**n= 1788**	**n= 457**	**n= 1868**	**n= 832**	**n= 57**
No/unknown	1758 (25)	61 (27)	194 (35)	123 (24)	150 (25)	1230 (25)	449 (25)	99 (22)	450 (24)	213 (26)	19 (33)
Yes	5156 (75)	169 (73)	361 (65)	395 (76)	459 (75)	3772 (75)	1339 (75)	358 (78)	1418 (76)	619 (74)	38 (67)

[a] From RA onset date to last visit date (negative durations and durations greater than age excluded).

[b] Patients may have missing information for one or more categories. Consequently, patient numbers for individual characteristics may be lower than total number of patients.

b/tsDMARD: biologic or targeted synthetic disease-modifying anti-rheumatic drugs; TNFi: tumor necrosis factor inhibitors; CCP: cyclic citrullinated peptide; ESR: erythrocyte sedimentation rate; RhF: rheumatoid factor; CRP: c-reactive protein.

Note: results for CCP, RhF, CRP and ESR are those recorded closest to RA onset date. Steroid use was recorded if a steroid was included in the list of used patient medications. CRP>500, CCP>600, RhF> 1000, age >100 years all defined as 'missing data.

Table 2 Number of patients receiving and ceasing first line b/tsDMARD treatment

	Rituximab	Tocilizumab	Tofacitinib	Abatacept	TNFis	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab
Started, n	230	555	518	609	5002	1788	457	1868	832	57
Stopped, n (%)	65 (28)	288 (52)	185 (36)	285 (47)	2560 (51)	862 (48)	250 (55)	948 (51)	466 (56)	34 (60)
Primary failure, n(%)[a]	21 (32)	57 (20)	124 (67)	97 (34)	964 (38)	307 (36)	108 (43)	344 (36)	194 (42)	11 (32)
[95% CI]	[21;45]	[15;25]	[60;74]	[29;40]	[36;40]	[32;39]	[37;50]	[33;39]	[37;46]	[17;51]

[a] Primary Failure was defined as stopping treatment within 6 months of treatment initiation. The percentage was relative to the subset that stopped treatment

Table 3 Reason for treatment cessation in patients who stopped all first-line b/tsDMARDs and patients classified as primary failures of first-line b/tsDMARDs.

All first line	Rituximab	Tocilizumab	Tofacitinib	Abatacept	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab
N[a] = 3383 patients	**N= 65**	**N= 288**	**N= 185**	**N= 285**	**N= 862**	**N= 250**	**N= 948**	**N= 466**	**N= 34**
n= 2656 Reasons	**n= 51**	**n= 238**	**n= 105**	**n= 233**	**n= 661**	**n= 221**	**n= 795**	**n= 327**	**n= 25**
Contra indication, n(%)	2 (4)	3 (1)	-	5 (2)	11 (2)	1 (0.5)	13 (2)	3 (1)	-
Lack of efficacy, n(%)	10 (20)	43 (18)	42 (40)	88 (38)	238 (36)	114 (52)	256 (32)	152 (47)	4 (16)
Uncertain, n(%)	6 (12)	11 (5)	4 (4)	10 (4)	27 (4)	3 (1)	32 (4)	4 (1)	-
Adverse reaction, n(%)	7 (14)	30 (13)	22 (21)	18 (8)	78 (12)	22 (10)	98 (12)	22 (7)	3 (12)
Miscellaneous, n(%)	26 (51)	151 (63)	37 (35)	112 (48)	307 (46)	81 (37)	396 (50)	146 (45)	18 (72)
Better Alternative	7 (14)	65 (27)	9 (9)	47 (20)	119 (18)	30 (14)	182 (23)	69 (21)	12 (48)
Completed treatment/no longer required	13 (26)	56 (24)	23 (22)	40 (17)	100 (15)	35 (16)	109 (14)	57 (17)	6 (24)
Financial Constraints	-	-	1 (1)	-	-	-	-	-	-
No Longer Available	-	-	-	-	-	-	-	-	-
Other	6 (12)	25 (11)	1 (1)	21 (9)	69 (10)	9 (4)	94 (12)	16 (5)	-
Patient non-adherence	-	5 (2)	3 (3)	4 (2)	192 (3)	7 (3)	11 (1)	4 (1)	-
	Rituximab	**Tocilizumab**	**Tofacitinib**	**Abatacept**	**Adalimumab**	**Certolizumab**	**Etanercept**	**Golimumab**	**Infliximab**

						pegol			
First line primary failureb	**N= 21**	**N= 57**	**N= 124**	**N= 97**	**N= 307**	**N= 108**	**N= 344**	**N= 194**	**N= 11**
N = 1263 patients	**n= 11**	**n= 50**	**n= 57**	**n= 72**	**n= 239**	**n= 92**	**n= 262**	**n= 139**	**n= 6**
n = 928 reasons									
Contra indication, n(%)	-	-	-	2 (3)	3 (1)	-	1 (0.4)	-	-
Lack of efficacy, n(%)	1 (9)	13 (26)	19 (33)	33 (46)	96 (40)	60 (65)	92 (35)	73 (53)	1 (17)
uncertain, n(%)	-	1 (2)	3 (5)	2 (3)	5 (2)	2 (2)	2 (1)	1 (1)	-
Adverse reaction, n(%)	-	10 (20)	12 (21)	9 (13)	38 (16)	9 (10)	51 (20)	12 (7)	2 (33)
Miscellaneous, n(%)	10 (91)	26 (52)	23 (40)	26 (36)	97 (41)	21 (23)	116 (44)	53 (38)	3 (50)
Better Alternative	2 (18%	10 (20)	7 (12)	10 (14)	31 (13)	5 (5)	47 (18)	20 (14)	2 (33)
Completed treatment/no longer required	5 (45)	9 (18)	12 (21)	8 (11)	36 (15)	11 (12)	25 (10)	28 (20)	1 (17)
Financial Constraints	-	-	1 (2)	-	-	-	-	-	-
No Longer Available	-	-	-	-	-	-	-	-	-
Other	3 (27)	7 (14)	-	8 (11)	29 (12)	3 (3)	38 (15)	5 (4)	-
Patient non-adherence	-	-	3 (5)	-	1 (0.4)	2 (2)	6 (2)	-	-

N is the number of patients who stopped treatment; "n" is the number of reasons for treatment cessation recorded; more than one reason for cessation could have been recorded for a patient; not all patient had a recorded reason. [b] Primary failure was defined as stopping treatment within 6 months of treatment initiation

Table 4 Kaplan-Meier estimates of persistence on second line b/tsDMARDs after discontinuation of first line TNF inhibitors due to "lack of efficacy"

	Persistence post primary failure of first line TNFi (N=309)					Persistence post-secondary failure of first line TNFi (N=429)				
	Rituximab	**Tocilizumab**	**Tofacitinib**	**Abatacept**	**TNFis**	**Rituximab**	**Tocilizumab**	**Tofacitinib**	**Abatacept**	**TNFis**
Total Patients, n(%)	13 (4)	49 (16)	25 (8)	92 (30)	130 (42)	13 (3)	74 (17)	54 (13)	88 (21)	200 (47)
Persistence at:										
6 months, %	75	78	71	61	60	83	70	58	70	64
12 months, %	75	57	ND	49	40	69	58	29	54	47
Median time to stopping (months) [95% CI]	49 [17; 74]	21 [11; 62]	21 [6; 21]	11 [8; 22]	9 [7; 12]	39 [9; ND]	24 [11; 43]	17 [5; ND]	14 [9; 24]	11 [9; 15]

ND: not determined

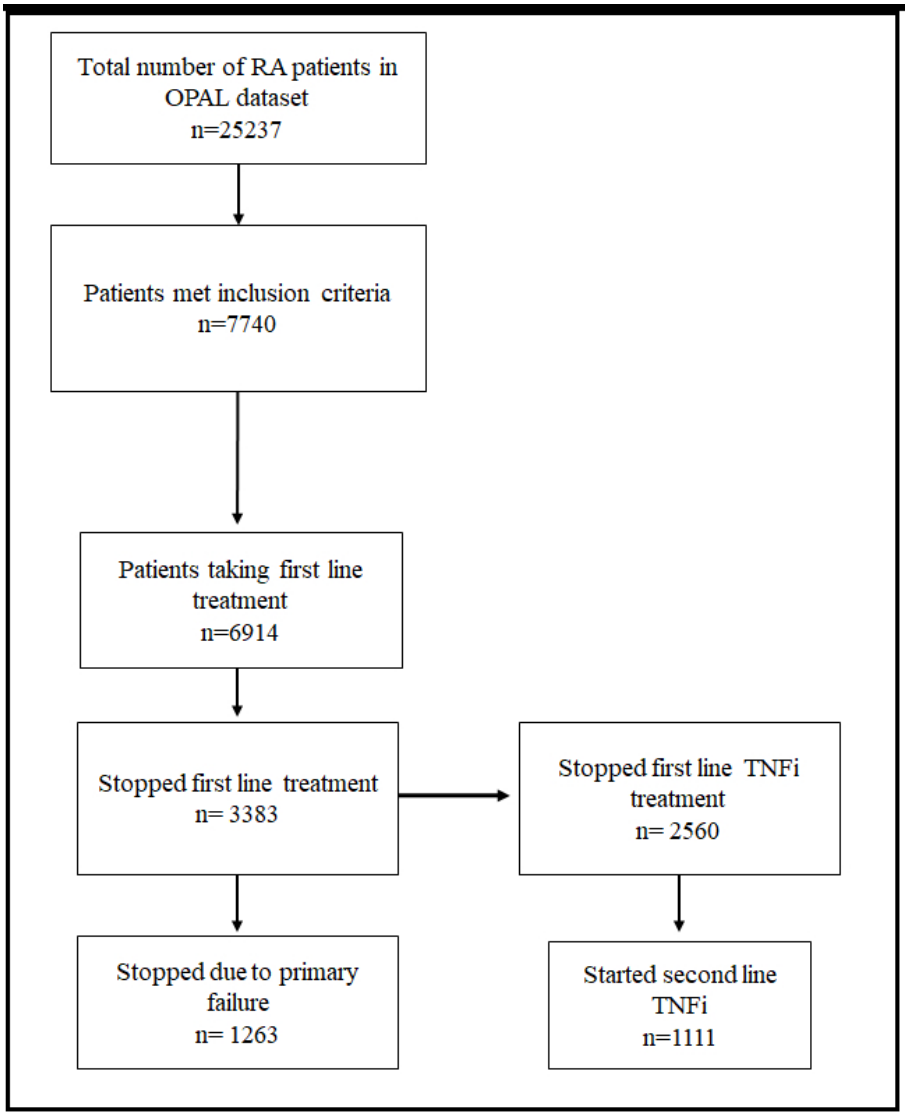

Figure 1: Flow diagram of rheumatoid arthritis patients in the OPAL dataset included in the study

Figure 1: Flow diagram of rheumatoid arthritis patients in the OPAL dataset included in the study

171x227mm (96 x 96 DPI)

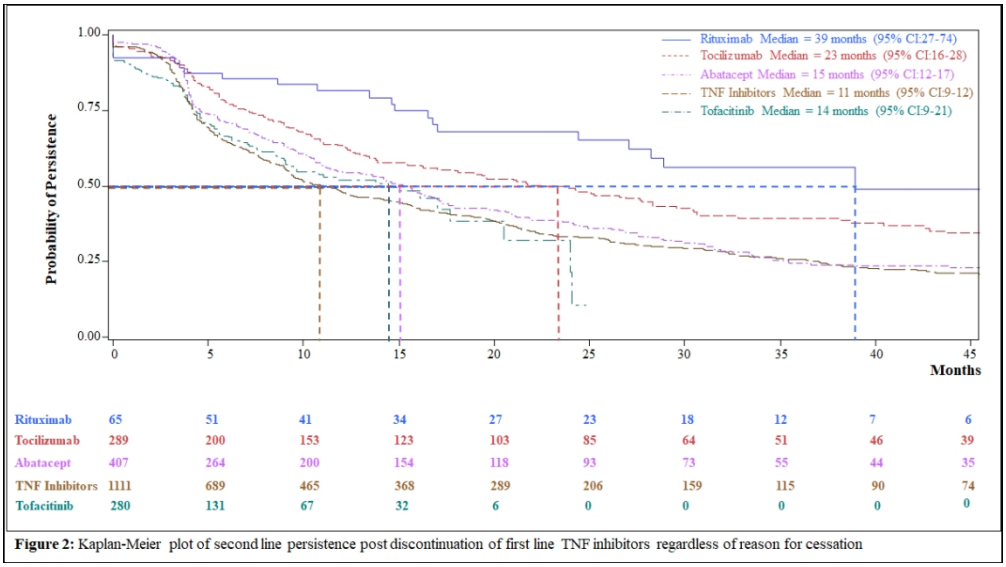

Figure 2: Kaplan-Meier plot of second line persistence post discontinuation of first line TNF inhibitors regardless of reason for cessation

Figure 2: Kaplan-Meier plot of second line persistence post discontinuation of first line TNF inhibitors regardless of reason for cessation

320x178mm (96 x 96 DPI)