

BMJ Open Adherence and dosing interval of subcutaneous antitumour necrosis factor biologics among patients with inflammatory arthritis: analysis from a Canadian administrative database

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To cite: Bhoi P, Bessette L, Bell MJ, *et al*. Adherence and dosing interval of subcutaneous antitumour necrosis factor biologics among patients with inflammatory arthritis: analysis from a Canadian administrative database. *BMJ Open* 2017;7:e015872. doi:10.1136/bmjopen-2017-015872

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2017-015872>).

Received 19 January 2017
Revised 7 August 2017
Accepted 8 August 2017



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ABSTRACT

Objectives Subcutaneous tumour necrosis factor alpha (TNF) inhibitors (SC-TNFis) such as golimumab (GLM), adalimumab (ADA), etanercept (ETA) and certolizumab pegol (CZP) have been used for many years for the treatment of inflammatory arthritis. Non-adherence to therapy is an important modifiable factor that may compromise patient outcomes. The aim of this analysis was to compare adherence and dosing interval of SC-TNFis in the treatment of people with inflammatory arthritis.

Design We used the IMS Brogan database combining both Canadian private and public drug plan databases of Ontario and Quebec. Target drugs included SC-TNFis for inflammatory arthritis. The index period was from 1 January 2010 to 30 June 2012 and patients were followed for 24 months through 30 June 2014. Inclusion criteria were adult patients newly prescribed a SC-TNFis with at least three prescriptions and retained on therapy at 24 months. Dosing regimens as per the product monographs were used to compare actual versus expected drug utilisation. The mean possession ratio was used as a marker for adherence. Patients who scored >80% were considered adherent. The average days between units was estimated by taking the total days on therapy and divided by the number of units the patient received.

Results 4035 patients were included: 683 (16.9%), 1400 (34.7%), 1765 (43.7%) and 187 (4.6%) were treated with GLM, ADA, ETA and CZP, respectively. The proportion of adherent patients in the GLM cohort (n=595/683, 87%, p<0.0001) was greater compared with ADA (n=1044/1400, 75%), ETA (n=1285/1765, 73%) and CZP-treated patients (132/187, 71%). In addition, the number of patients receiving biological drug at a shorter dosing interval was similar between cohorts, and was 5%, 6%, 12% and 4% in GLM (≤26 days), ADA (≤12 days), ETA (≤6 days) and CZP-treated patients (≤12 days), respectively.

Conclusions In this real-life administrative database, GLM had better adherence compared with other SC-TNFis.

INTRODUCTION

Inflammatory arthritis (IA), including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS), is

Strengths and limitations of this study

- The strengths of this study are its large sample size and generalisation since it includes over half of the overall Canadian population of inflammatory arthritis patients.
- Limitations include the absence of clinical data, inability to match cohorts and the potential for administrative coding errors.
- There is also a potential for selection bias since patients had to be on therapy for two years to be included in the analysis.

characterised by severe pain, inflammation, progressive joint damage and decline of physical function over time. More aggressive treatment approaches in the last two decades have led to improved patient outcomes and prevention of disability. The breakthrough in the treatment of IA happened with the introduction of biologics, specifically tumour necrosis factor alpha inhibitors (TNFis) in the late 1990s and early 2000s. More recently, biologics with other mechanisms of action were introduced and became available to rheumatologists.^{1 2} However, TNFis remain the most widely used biologics in rheumatology due to many years of clinical experience and provincial reimbursement criteria in Canada.

However, any treatment, no matter how advanced, would only work if taken by a patient in accordance with the prescription. According to the WHO: 'Across diseases, adherence is the single most important modifiable factor that compromises treatment outcomes'. Indeed, poor adherence to treatment in RA has been shown to have negative impact on patient outcomes.^{3 4}

In practice, adherence to treatment reflects the extent to which a medication is taken as prescribed. A number of studies have shown that adherence to treatment is generally poor across chronic diseases: approximately 50% of all patients with chronic medical conditions do not adhere to their prescribed medication regimens.⁵ In patients with RA, for example, adherence to disease-modifying antirheumatic drugs has been shown to be anywhere from 30% to 80%, depending on the study and methodology used.⁶ Adherence to biological medications in RA has also shown variability ranging from 11% to 88%.^{7–10} The observed differences in results of those studies can be at least partly explained by the absence of a reference standard measure of adherence and wide variability of its definition and terminology. One of the most commonly used measures of adherence is the medication possession ratio (MPR).^{11 12} MPR ≥ 0.8 (or 80%) is a widely used threshold of adherence,^{13–17} though more recent studies suggested that an MPR of 90% or above may be a better threshold for deeming consumption as 'adherent'.¹⁸

Several factors can potentially influence patient adherence to therapy, including healthcare system factors (access to therapy), patient–provider relationship, patient-related factors (eg, age, sex, education, socioeconomic status, beliefs about disease and treatment) and therapy-related factors (eg, efficacy, tolerability, convenience, mode/frequency of administration and costs).⁶

All subcutaneous (SC)-TNFis, including golimumab (GLM), adalimumab (ADA), etanercept (ETA) and certolizumab-pegol (CZP), are available in Canada and are approved for the treatment of RA, AS and PsA. The purpose of this analysis was to compare the adherence to treatment and dosing intervals of SC-TNFis among patients with IA.

METHODS

Data sources

Data for this analysis was derived from a health administrative database from IMS Brogan, a privately owned company collecting drug utilisation data now part of QuintilesIMS. Those include data from the National private drug plans (PDP) database as well as the public drug plans database for the provinces of Ontario and Quebec (OPDP and Regis de l'Assurance Maladie du Quebec (RAMQ), respectively) in Canada. The data were also completely void of identifying information which precluded the need to obtain ethics approval. The raw data used for this study can be obtained by contacting the owner of the database (IMS Health Consulting). The analysis report used for this manuscript can be provided by communicating with FN.

Patient population selection

Adult patients (age ≥ 18 years) starting treatment with one of the SC-TNFis (GLM, ADA, ETA or CZP) from 1 January 2010 to 30 June 2012 for the indication of RA, AS or PsA were identified. Time of initiation treatment

with a SC-TNFi served as the index date, and patients were followed up for 24 months. Eligible patients for this analysis were required to remain on the initiated therapy for a minimum of 24 months following the index date. Patients were identified as retained on therapy if the following two criteria were met: patients had at least three prescriptions of a target SC-TNFi and the number of days from the start of the patients first prescription of a target SC-TNFi to the end of the last prescription, including the days of supply of the last prescription, equalled to or exceeded the length of the follow-up period.

Measures

The recommended dosing regimens for the treatment of IA, as per the Canadian product monographs^{19–22} were used to compare actual versus expected drug use for each SC-TNFi. The dosing regimens for each SC-TNFis are the same between indications and are as follows: 50 mg monthly for GLM¹⁹; 40 mg every other week for ADA²² and 50 mg weekly for ETA.²¹ For CZP, the recommended regimen includes a loading dose of 400 mg at weeks 0, 2 and 4 and a maintenance dose of either 400 mg every 4 weeks or 200 mg every 2 weeks.²⁰ All biologics compared in this study are usually supplied 1 month at a time—GLM is supplied as one dose in a box, ADA as two doses, ETA as four in a box and certolizumab as two in a box.

The compliance rate was calculated by dividing the 'estimated days' supply in the defined period' by the 'number of days in the defined period'. However, 'days' supply information is not reliable for biological drugs; thus, it was estimated based on total drug use in the defined period. Patients who dose escalated were identified and their days of supply were calculated based on their escalated dosing, so as not to overestimate the adherence. Adherence to a prescribed SC-TNFi was measured by the MPR.^{11 12} Patients who scored $>80\%$ were considered adherent as per the most commonly accepted definition.^{14–16 23}

In addition to the unadjusted analyses carried out on the full study population, analyses of adherence were also carried out on cohorts matched by the line of biological therapy, attempting to adjust for potential selection bias. Proportions of patients on first, second, third and fourth line of biological therapy were identified in each cohort. MPR was then calculated based on line of therapy.

For the analysis of dosing interval, the target SC-TNFis were standardised in units based on dosing regimen as per the following: a unit is a syringe or phial; one unit of GLM, ADA, ETA and CZP is 50 mg, 40 mg, 50 mg and 200 mg, respectively. The total amount of a target SC-TNFi (in mg) dispensed per patient was then calculated in units. The average number of days between units was estimated by taking the total days on therapy and dividing by the number of units the patient received.

Statistical analysis

p Values obtained from χ^2 and pair-wise comparison tests for statistical differences on the proportion of adherent

Table 1 Medication possession ratio

Measure	GLM	ADA	ETA	CZP	p Value versus GLM
N	683	1400	1765	187	
MPR, mean (SD)	0.90 (0.14)	0.85 (0.18)	0.84 (0.20)	0.84 (0.16)	<0.0001*
MPR ≥0.80, n (%)	595 (87%)	1044 (75%)	1285 (73%)	132 (71%)	<0.0001†

*p Value obtained from one-way analysis of variance for multiple means comparison.

†p Value obtained from χ^2 and pair-wise comparison tests for statistical differences on the proportion of high adherent patients.

ADA, adalimumab; CZP, certolizumab pegol; ETA, etanercept; GLM, golimumab; MPR, medication possession ratio.

patients were carried out. A p value <0.05 was considered to be statistically significant.

RESULTS

The final study population was 4035 patients, including 683 for GLM cohort (16.9%), 1400 for ADA cohort (34.7%), 1765 for ETA cohort (43.7%) and 187 for CZP cohort (4.6%). The distribution of the study population by data source was as follows: 2509 (62.2%) from PDP National, 634 (15.7%) from RAMQ and 892 (22.1%) from OPDP.

Adherence analysis

Table 1 provides the MPR measures for each target SC-TNFi. The proportion of adherent patients (MPR ≥0.80) was significantly higher for GLM cohort: 87% versus 75% for the ADA cohort, 73% for ETA cohort and 71% for CZP cohort (p<0.0001 for all cohorts vs GLM). Distribution of patients by MPR within each SC-TNFi cohort is shown in figure 1. The proportions of patients with the MPR ≥90% were as follows: 70%, 54%, 54% and

Table 2 Patient distribution by biological line experience; n (%)

Index drug	Bionaive (%)	Second line (%)	Third line (%)	Fourth line (%)
CZP	169 (90.4)	16 (8.6)	2 (1.1)	0 (0.0)
ETA	1669 (94.5)	88 (5.0)	7 (0.4)	1 (0.1)
ADA	1322 (94.4)	76 (5.4)	2 (0.1)	0 (0.0)
GLM	586 (85.8)	94 (13.8)	1 (0.1)	2 (0.3)

ADA, adalimumab; CZP, certolizumab pegol; ETA, etanercept; GLM, golimumab.

45% in GLM, ADA, ETA and CZP cohorts, respectively. The same pattern of results was observed when cohorts were compared by the mean MPR where the GLM cohort had a higher mean MPR (0.90, p<0.0001) compared with all other cohorts which were similar between each other with a mean MPR of 0.85, 0.84 and 0.84 for the ADA, ETA and CZP cohorts, respectively. Additional analyses were carried out to limit potential biases. Table 2 provides the patient distribution by line of therapy within each target SC-TNFi cohort. The vast majority of patients (between 85.8% and 94.5%) in all treatment cohorts were bionaive with a target SC-TNFi as the first-line biological therapy. However, the proportion of bionaive patients was lower in the GLM cohort (85.8%) than in other cohorts (94.4% for ADA cohort, 94.5% for ETA cohort and 90.4% for CZP cohort). To determine if the line of therapy had an impact on adherence, the proportion of adherent patients (MPR ≥0.80) was calculated in the total study population and in cohorts based on the line of biological therapy. The proportion of adherent patients was the same (76%), in both the bionaive and bioexperienced cohorts. The analysis was also performed in bionaive patients only, and the results were almost identical to the unadjusted analysis: the proportion of adherent patients (MPR ≥0.80) were 88% for GLM cohort, 75% for ADA

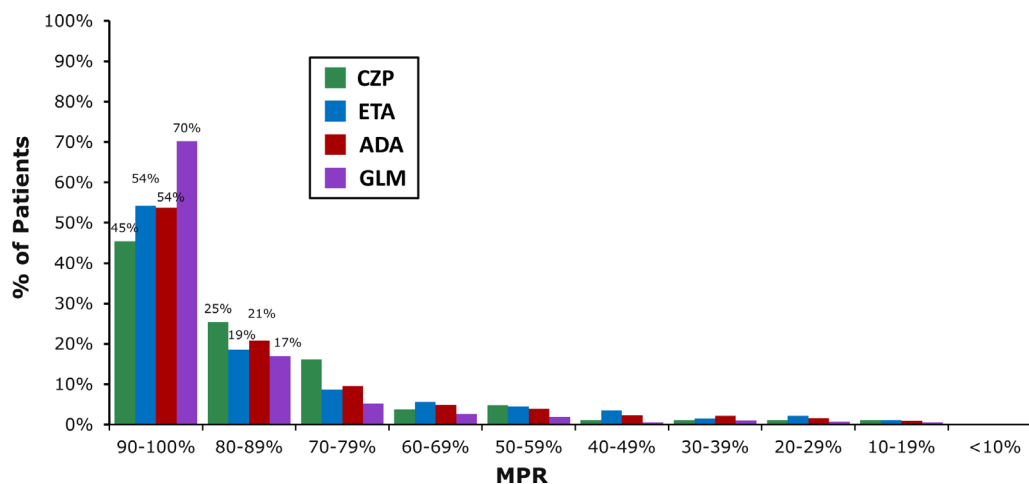


Figure 1 Distribution of patients by MPR within each SC-TNFi cohort. ADA, adalimumab; CZP, certolizumab pegol; ETA, etanercept; GLM, golimumab; MPR, medication possession ratio; SC-TNFi, subcutaneous tumour necrosis factor-alpha inhibitors.

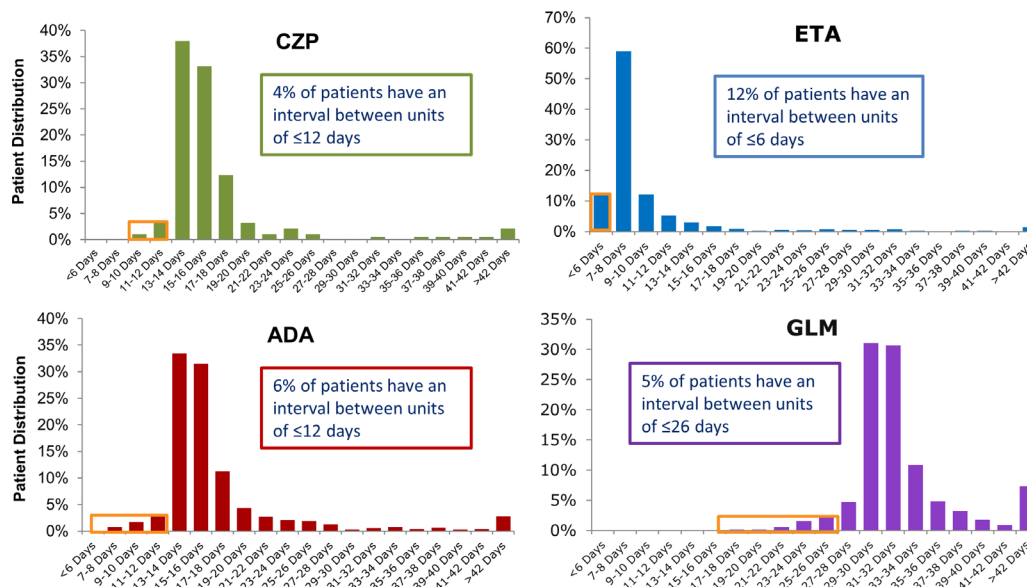


Figure 2 Patient distribution per average days elapsed between units. ADA, adalimumab; CZP, certolizumab pegol; ETA, etanercept; GLM, golimumab.

cohort, 72% for ETA cohort and 71% for CZP cohort ($p < 0.0001$ for all cohorts vs GLM).

Dosing interval analysis

Figure 2 shows the distribution of patients per average days elapsed between units. About two-thirds of patients in each cohort had an average time elapsing between units within the recommended dosing interval ± 1 day. The remaining third of patients in each cohort had their average dosing interval shorter or longer than recommended by the respective product monographs. To investigate the number of patients receiving their target SC-TNFi more frequently than it is recommended by the product monograph, the following definitions of shorter than recommended dosing interval were assumed based on the dosing regimen for each target SC-TNFi: ≤ 6 days for ETA (1 day shorter than the recommended regimen of once weekly),²¹ ≤ 12 days for ADA and CZP (2 days shorter than the recommended regimen of every other week)^{20 22} and ≤ 26 days for GLM (4 days shorter than the recommended regimen of once monthly).¹⁹ The proportions of patients in each cohort receiving their SC-TNFi more frequently than recommended by the PM were comparable between the cohorts: 6% for ADA, 12% for ETA, 4% for CZP and 5% for GLM.

DISCUSSION

One of the major challenges in the treatment of chronic medical conditions, such as IA, is optimising patient adherence to therapy, as the implications of non-adherence can be far reaching in terms of reducing treatment effectiveness and increasing healthcare costs.^{3 4 24-27} The objectives of this study were to compare the adherence to treatment and dosing intervals of SC-TNFis, including GLM, ADA, ETA and CZP, among patients with IA. The higher proportion of ETA and ADA patients may reflect

the fact that GLM and CZP were introduced much later to the Canadian market. Adherence measures were assessed during the study period as well as the dosing intervals.

Overall, we found a considerably high adherence rates to SC-TNFis (76% of adherent patients), which is in agreement with some of the previous studies of adherence to biologics in RA.^{7 10} It is possible that this is due to the fact that patient had to be on therapy for 2 years to be included in this analysis. This window was selected to ensure appropriate follow-up time to assess adherence and to remove the potential impact of primary non-response to therapy. Significant differences were identified in adherence measures between the study cohorts. Our analysis showed that GLM patients had significantly higher rates of medication adherence as measured by the mean MPR and proportions of adherent patients (MPR $\geq 80\%$) compared with all other study cohorts.

Those results are in agreement with a US study by^{10 10} which compared a number of adherence and use measures in a population of patients with RA starting treatment with a SC-TNFi using deidentified medical information from insurance databases in the USA. Those results were interpreted by the authors as being in agreement with previous findings of patient preferences and better adherence to medications with longer versus shorter dosing intervals²⁸⁻³⁰ and supported the inverse relationship between dosing frequency and adherence reported in various studies with different medication classes.³¹⁻³³ This relationship was also confirmed in our study, as golimumab is the only SC-TNFi on the market with a once-monthly dosing regimen.

Noteworthy, the GLM cohort had a slightly higher proportion of bioexperienced patients comparing to other cohorts in our study, possibly due to its later introduction into the Canadian market and the fact that a trial in TNF failures was available.³⁴ Nonetheless, sensitivity

analyses showed that line of therapy had no impact on adherence.

Dosing interval for SC-TNFis was evaluated in our study with the objective to assess the proportion of patients whose treatment needed to be intensified (ie, by shortening of the dosing interval) during the course of a 2-year follow-up. We found that shortening of the dosing interval was observed in all the SC-TNFi cohorts and that the proportions of patients were comparable between the four drugs. To the best of our knowledge, this is the first detailed report on shortening of the dosing interval across different SC-TNFis. Though a number of studies have reported the dose escalation for SC-TNFis, ranging from 0.4%–5% for ETA and 7%–24% for ADA,^{35–40} comparison with our results would be difficult since those studies mostly evaluated increases in mean dosage per given time period as a measure of dose escalation.

Poor adherence has been linked to suboptimal patient outcomes across chronic diseases, including IA,^{3 4 25} and biological therapy is no exception from this relationship. A study by Bluett *et al*⁴ and Blume *et al*³⁶ showed that patients who were ever non-adherent to their SC-TNFis were significantly less likely to achieve a good European League Against Rheumatism response and significantly more likely to have no response after 6 months of treatment.

The limitations of this study are as follows. First, as the clinical data were unavailable from the administrative database, the treatment cohorts were not matched for patient and clinical characteristics; meaning that there could be other unmeasured factors that would drive use and adherence patterns associated with each medication. Indeed, the proportion of patients with RA, AS and PsA in each cohort cannot be ascertained. The selection of a 24 months' period on therapy also could lead to a channelling bias and preselect patients with better adherence and overall response to therapy. An additional limitation for the data source is the fact that it may include administrative coding errors. Finally, one could argue that pharmacy refills do not necessarily mean that the medication was in fact taken by a patient.

In conclusion, this real-life study evaluating adherence to SC-TNFis in IA using data from the Canadian administrative databases, demonstrates considerably high adherence rates with SC-TNFis. However, GLM was found to have better adherence compared with the other SC-TNFis, which could, in part, be the result of a simpler, less frequent dosing regimen. Further studies are needed to investigate the reasons for the difference in adherence between golimumab and other SC-TNFis and to evaluate the impact of this improved adherence on clinical and health-economic outcomes.

Contributors PB was involved in the design and acquisition; PB, FN and KM in the analysis; PB, MJB, LB, CT, FN and KM in the interpretation and FN and KM in the writing.

Funding This study was funded by Janssen, Canada funded this study. PB, KM, CT and FN are employees of Janssen, Canada. Study sponsors assisted with study design, interpretation of results and manuscript development.

Competing interests PB, CT, FN and KM are (were) employees of Janssen when the study was executed.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The raw data used for this study can be obtained by contacting the owner of the database (IMS Health Consulting). The analysis report used for this manuscript can be provided by communicating with FN.

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