

Claims Data Analysis of Tumor Necrosis Factor Inhibitor Treatment Dosing Among Patients with Rheumatoid Arthritis: A Systematic Review of Methods

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Abstract

Background With tumor necrosis factor inhibitors, changes of dosing, switching between drugs, insufficient adherence, and persistence are frequent in rheumatoid arthritis. Because this is often associated with decreased efficiency and increased costs, dosage analyses based on claims data are of increasing interest for healthcare providers and payers. Nevertheless, no standardized methods exist to ensure high-quality research.

Objective In this review, we compare and discuss applied methods in claims data-based dosage analyses of tumor necrosis factor inhibitor prescriptions in patients with rheumatoid arthritis.

Methods A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. The dosage

analysis methods performed within the selected studies were classified into switching, persistence, adherence, and dosage-change analyses, and were then compared and finally discussed.

Results A total of 45 studies were found to be relevant. In most studies, a change in dose or persistence was evaluated, followed by switching and adherence analyses. Analyses of changed dose exhibit the most extensive variation of methods. We divided them into three principal methods, where a specified reference dose is compared with (1) the last dose, (2) any dose, or (3) all doses.

Conclusion The systematic review identified a high variation of methods. Our results may be helpful for choosing appropriate methods in future studies. The results also demonstrate the need for evidence-based recommendations of methods used in claims data research.

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Key Points

Dosage analyses of switching differ with respect to the implementation of a time frame and with respect to controlling the discontinuation of the previous therapy.

Dosage analyses of persistence are characterized by the criteria used for therapy discontinuation. These are allowance of switching to other treatments and the therapy discontinuing prescription gap.

Proportion of days covered and the medication possession ratio with fixed or variable follow-ups are the most frequently used methods for claims data analyses of adherence.

Dosage change analyses exhibit the most extensive variation of methods. They differ with respect to the type of dose comparison and with respect to other restrictions that are necessary to define a dose escalation or a decrease in dose. These restrictions refer for example to the length of prescription intervals and to the difference between a changed dose and its reference.

We divide changes in dose into three principal methods: a comparison of (1) the last dose, (2) any dose, or (3) all doses to a specified reference dose. Reference doses are the index, maintenance, recommended, and previous dose.

1 Introduction

Tumor necrosis factor (TNF) inhibitors are substantial components in the management of patients with rheumatoid arthritis (RA). RA is a systemic, inflammatory, chronic autoimmune disease of the peripheral joints. It leads to joint swelling and pain with decreasing mobility. The messenger substance TNF- α triggers the inflammatory process of RA. Because TNF-inhibitors are able to block TNF- α itself or the receptors of the target cells, they can influence the inflammatory process directly, reduce the progression of the disease, and improve symptoms [1]. Inadequate compliance or adherence to therapy could complicate the therapeutic success and cause higher therapy costs [2]. TNF inhibitors are costly and changes in prescription may significantly impact healthcare costs [3, 4]. Therefore, investigating changes in therapy is important to patients, healthcare providers, and healthcare payers. Because claims data analyses allow for insight into drug prescriptions under real-life conditions,

they are powerful instruments for evaluating healthcare provision [5].

High-quality research is needed to provide good evidence on comparative drug dosing analyses in real life, but there are no standardized methods available. No systematic review has been conducted that classifies and compares methods used in studies reporting dosage analyses of TNF inhibitor prescriptions in patients with RA on the basis of claims data. Therefore, the objective of the present study is to provide such a review, comparing the methods used in switching, persistence, adherence, and dosage-change analyses. Finally, the resulting findings may provide guidance for the most appropriate application of the methods in future research and contribute to evidence-based recommendations for dosage analyses with claims data.

This review is structured as follows: first, we present the methodology of our review, comprising the eligibility criteria, the search strategy, and the handling of outcomes and data. Second, we present an overview of the identified studies and their characteristics, followed by classification of their methods. We end with a discussion of the identified methods.

2 Methods

To identify the relevant literature, a systematic review following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was conducted on February 12, 2016. First, the selection criteria were defined. Second, a systematic search, based on these selection criteria, in the MEDLINE, BIOSIS Previews, EMBASE Alert, EMBASE, German Medical Science—Journals and Meetings and SciSearch databases, provided by the German Institute for Medical Documentation and Information [6] platform, was performed. Search terms used corresponded to the indications (RA), the intervention (TNF inhibitors), claims data, and dosage analyses, as well as their results, such as changes in dose, switching, adherence, and discontinuation. Synonyms for each term in either the German or the English language were used. Sub-searches for each search term were applied and finally combined. The full search code can be provided on request. From the identified literature, the relevant studies were selected based on the following inclusion criteria:

1. Studies must be full publications written in either the German or the English language.
2. The study population must include at least one subgroup of RA patients.
3. The analyses must be based on claims data.
4. The course of drug therapy, such as switching drugs, changes in dosage, adherence, or persistence, must be investigated.

5. The therapy must involve at least one TNF inhibitor.
6. The dosage analyses must be an essential part of the study, meaning outcomes of the dosage analyses must be reported.

The comparison of methods is basically a comparison of different claims data-based definitions of the various outcomes. To this end, the identified studies were classified into their outcomes of the switching, adherence, persistence, and dosage-change analyses.

Switching analysis was classified based on the time frame and information on whether discontinuation of the former drug was ensured. The time frame is the gap between the last prescription of the former drug and the new one that is allowed at maximum, before a therapy is considered to be terminated.

We use the terms persistence and adherence in accordance with the International Society of Pharmacoeconomics and Outcome Research because the terms adherence and persistence are not used consistently in the identified literature [7]. According to the International Society of Pharmacoeconomics and Outcome Research, persistence describes the duration of continuous treatment. Methods of persistence analyses are classified by the maximum time frame allowed and information on whether a switch between drugs within a drug class was accepted. The time frame is the maximum prescription gap that was still allowed between two prescriptions to assume persistence. Otherwise the therapy was considered to be terminated.

In contrast to persistence, adherence is a measure of the extent to which a patient adheres to his/her treatment as recommended or prescribed. It is typically bound to a value between 1 and 0, where 1 indicates perfect adherence, and 0 indicates no adherence. We classified adherence analyses based on the measure of adherence that was used in the identified literature.

A changed dose is deemed as either an increase or decrease in prescription dose. For dosage change analyses, we defined three principal methods based on the type of doses that were compared. These are (1) the last dose vs. reference, (2) any dose vs. reference, and (3) all doses vs. reference. In studies being selected to category (1), any change or a certain minimum change of the last prescription dose within the follow-up, compared with a reference dose was defined as a dose escalation or dose reduction. In category (2), all doses within the study period were compared with a reference. If any change in dose, as defined in the corresponding study, can be observed, the associated patient was flagged as having had a dose escalation or dose reduction. In category (3), mean doses of all prescriptions within a certain period were calculated and compared with a reference. The periods chosen varied.

A quantitative assessment of quality, in terms of validity and sensitivity, exceeds the scope of this review and should be subjected to further research.

3 Results

3.1 Search Results

The process of selecting references included in this review is shown in Fig. 1. After excluding duplicates and articles not complying with the inclusion criteria, 45 studies were included in the present review. An overview of the selected publications is given in Table 1. In most studies, treatment with adalimumab (ADA), etanercept (ETN), and/or infliximab (IFX) was evaluated. Because golimumab (GLM) and certolizumab pegol (CP) have only been available since 2009, there are only a few dosage analyses available in recent studies. No study analyzing dosing of biosimilars was found. In most studies, the change in dose ($n = 27$) or persistence ($n = 26$) was evaluated, followed by switching analyses ($n = 20$). Adherence was only investigated in 14 studies. The claims data of the studies identified were mostly generated from different US databases. Only four of them used Korean, Swiss, German, or Italian claims data [4, 8–10].

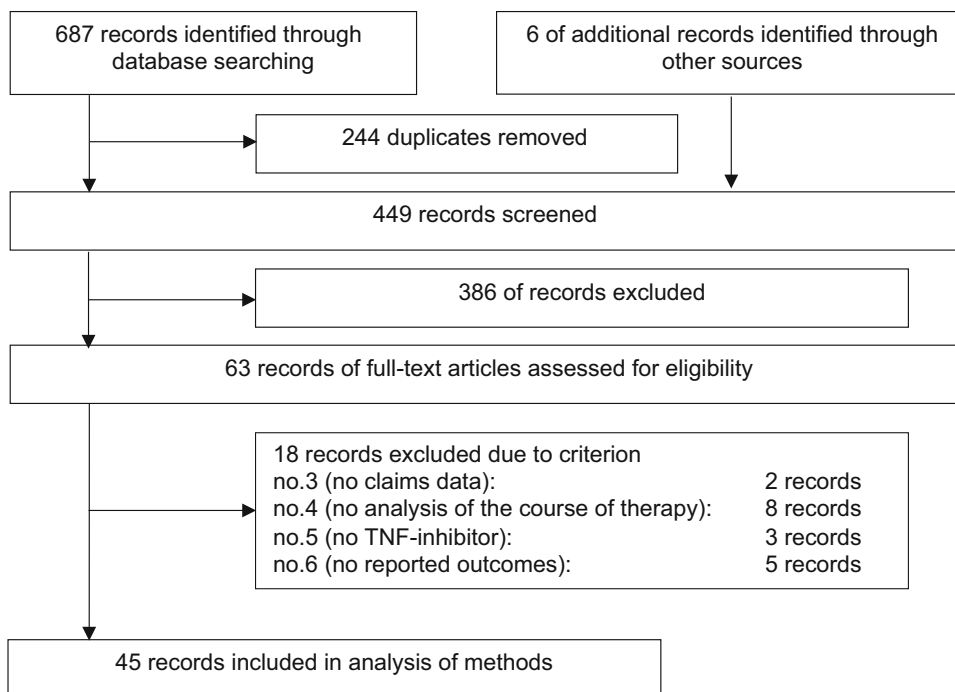
3.2 Definitions of Switching, Persistence, and Adherence

3.2.1 Switching

Switching of therapy influences persistence because it often terminates the current treatment. Available studies explored either switching or they attempted to analyze characteristics of subgroups of people who switched drugs [11]. A switch is defined as a change between certain medications. Some studies defined a maximum time frame of various lengths between the last prescriptions of the former drug and the prescription of the new drug. The switch needs to take place within that frame, otherwise the therapy is considered to be terminated. Some studies also indicated if they had ensured the discontinuation of the former drug to avoid confusing co-medication with switching. The various definitions applied are shown in Table 2.

The termination of the previous therapy was assured in five studies [8, 9, 12–14]. Most studies did not make any statement regarding termination of previous therapy. A maximum time frame was rarely specified. The length of this period mostly depends on the days of supply (DOS)¹ of

¹ DOS are either given in the claims data or they refer to the expected prescription interval.

Fig. 1 Process of selection

the last prescription of the former medication plus an additional period of 30 or 90 days [9, 13, 15]. In one case, a time frame of 200 % of the prescribed index-DOS was chosen instead [16]. In contrast, in four cases, a time frame was not required [17–20]. It should be noted that most studies did not indicate whether or not a time frame was implemented.

3.2.2 Persistence

A therapy is terminated either if a switch to another medication occurs or the time frame, meaning the gap between two prescriptions, gets too large. Table 3 lists the allowable switches between medications and which time frames were accepted for the assumption of persistency. With the exception of Curkendall et al., who evaluated persistence for several drugs simultaneously, no other authors explicitly allowed a switch in medication [21]. The accepted gap between two prescriptions mostly depends on DOS or the expected dosing intervals plus a further period of 30–90 days. Expectations are usually drawn from the therapy recommendations. In contrast, a fixed maximum period was defined in six studies [8, 19, 20, 22–24].

3.2.3 Adherence

Adherence is sometimes difficult to evaluate in claims datasets because most TNF inhibitors are injected by the patients themselves, and thus detailed information is missing in the database. This is not the case with IFX,

which is by intravenous (i.v.) application in a clinical setting. Therefore, this is registered in the claims data. In either case, it can be observed whether the prescriptions are refilled within DOS-supplied or within recommended intervals. Thus, the fraction of days with medication on hand can be determined, which is fundamental for the calculation of measures of adherence.

For the most part, adherence was examined with ratios such as the medication possession ratio (MPR) [2, 12, 21, 22, 25–28], the proportion of days covered (PDC) [13, 22, 23, 28, 29], or the compliance ratios of Harley et al. or Tkacz et al. [30, 31]. In contrast to the MPR, which equals the sum of DOS divided by the treatment period, the PDC considers the days with DOS available to the patient by taking the storability of drugs into account.

The MPR was calculated for fixed [2, 25] or variable follow-ups [12, 21, 22] with

$$\text{MPR} = \frac{\sum_{t=0}^{T_f} \text{DOS}}{T_f},$$

where T_f indicates the follow-up. Variable follow-ups depend on individual treatment periods. The treatment usually starts with the index date, the date of the first prescription and ends with the end of study period or with the termination of the treatment, whereas fixed follow-ups are the same for all patients. In that case, the length of the follow-up is specified ex ante. Only patients who are persistent within that period are analyzed. With fixed

Table 1 Overview of selected publications according to the prescribed TNF inhibitors and the mode of change in dosing

Author [ref.], year	TNF inhibitors					Mode of change in dosing: switching (S), persistence (P), adherence (A), change (C)				Source of claims data	
	IFX	ADA	ETN	GLM	CP	S	P	A	C	Provider	Country
Harley et al. [30], 2003	x		x					x	x	A large health plan	USA
Gilbert et al. [38], 2004	x		x						x	IMS PharMetrics	USA
Berger et al. [32], 2005	x								x	Constella	USA
Etemad et al. [42], 2005	x		x						x	A large health plan	USA
Ollendorf et al. [46], 2005	x								x	IMS PharMetrics	USA
Weycer et al. [11], 2005	x		x						x	Constella	USA
										Ingenix LabRx	
Grijalva et al. [12], 2007	x	x	x			x	x	x		Tennessee Medicaid	USA
Curkendall et al. [21], 2008		x	x				x	x		MarketScan	USA
Tang et al. [47], 2008	x	x	x				x	x		IMS PharMetrics	USA
Wu et al. [34], 2008	x	x	x				x		x	Ingenix employer database	USA
Borah et al. [2], 2009		x	x				x	x		A large health plan	USA
Nair et al. [43], 2009	x								x	MarketScan	USA
Ollendorf et al. [33], 2009	x	x	x						x	IMS PharMetrics	USA
Yazici et al. [15], 2009	x	x	x			x	x		x	IMS PharMetrics	USA
Gu et al. [48], 2010	x	x	x						x	MarketScan	USA
Harrison et al. [3], 2010	x	x	x				x		x	IMS PharMetrics	USA
Huang et al. [41], 2010		x	x						x	MarketScan	USA
Li et al. [13], 2010	x		x			x	x	x		Medicaid Analytic Extract	USA
Ogale et al. [17], 2011	x	x	x			x	x		x	Optum Insight	USA
Bolge et al. [40], 2012	x								x	HIRD	USA
										IMS LifeLink	
										PPD	
										WKPS	
Bonafede et al. [49], 2012	x	x	x			x	x			MarketScan	USA
Cho et al. [8], 2012	x	x	x			x	x			Korea National Health Insurance claims database	Korea
Nguyen-Khoa et al. [50], 2012	x	x	x			x				MarketScan	USA
Thyagarajan et al. [51], 2012	x	x	x			x	x			Optum Insight	USA
Zeidler et al. [4], 2012	x	x	x				x		x	Helsana Health Insurance	Switzerland
Blume et al. [44], 2013		x	x				x		x	Medco	USA
Chastek et al. [37], 2013	x	x	x						x	Optum Insight	USA
Fisher et al. [39], 2013	x	x	x			x	x		x	HIRD	USA
Johnston et al. [18], 2013	x	x	x			x				MarketScan	USA
Curtis et al. [25], 2014a	x	x	x	x		x		x	x	IMS PharMetrics	USA
Curtis et al. [26], 2014b	x	x	x	x		x		x	x	MarketScan	USA
Howe et al. [14], 2014	x	x	x	x	x	x	x			Humana Health Insurance	USA
Joyce et al. [36], 2014	x	x	x				x		x	IMS LifeLink	USA
Meissner et al. [16], 2014	x	x	x			x				IMS PharMetrics	USA
Neubauer et al. [9], 2014	x	x	x			x	x		x	DAK Health Insurance	Germany
Oladapo et al. [27], 2014	x	x	x			x		x	x	Texas Medicaid	USA
Tkacz et al. [22], 2014		x	x	x			x	x		Optum Insight	USA
Wu et al. [24], 2014	x	x	x	x	x	x	x			Medco	USA
Bonafede et al. [23], 2015	x	x	x	x	x	x	x	x	x	MarketScan	USA

Table 1 continued

Author [ref.], year	TNF inhibitors					Mode of change in dosing: switching (S), persistence (P), adherence (A), change (C)				Source of claims data	
	IFX	ADA	ETN	GLM	CP	S	P	A	C	Provider	Country
Curtis et al. [28], 2015	x	x	x	x	x	x		x	x	Optum Research	USA
Johnston et al. [20], 2015	x						x			MarketScan	USA
Sangiorgi et al. [10], 2015	x	x	x	x			x		x	Health-Assisted Subjects Database	Italy
Tkacz et al. [31], 2015	x						x	x		Optum Insight	USA
Zhang et al. [29], 2015	x	x	x				x	x		Medicare	USA
Harnett et al. [19], 2016	x	x	x	x	x	x	x			MarketScan	USA
Total	40	34	39	9	5	20	26	14	27		

ADA adalimumab, CP certolizumab pegol, ETN etanercept, GLM golimumab, HIRD HealthCore Integrated Research Database, IFX infliximab, PPD Premier Perspective Database, TNF tumor necrosis factor, WKPS Wolters Kluwer Pharma Solutions, x applied in analysis

Table 2 Definitions of switching

Time frame	Discontinuation ensured?	
	Yes	Not specified
Not specified	Cho et al. [8]	Bonafede et al. [49]
		Nguyen-Khoa et al. [50]
		Thyagarajan et al. [51]
		Fisher et al. [39]
		Curtis et al. [25]
		Curtis et al. [26]
		Neubauer et al. [9]
		Oladapo et al. [27]
		Wu et al. [24]
		Bonafede et al. [23]
No time frame	Harnett et al. [19]	Ogale et al. [17]
		Johnston et al. [18]
		Johnston et al. [20]
		Yazici et al. [15]
30 days + DOS	Howe et al. [14]	
45 days		
90 days + DOS	Grijalva et al. [12]	
	Li et al. [13]	
200 % × DOS ^{index}		Meissner et al. [16]

DOS days of supply, DOS^{index} DOS of index prescription

follow-ups, the end of the follow-up can be exceeded by DOS_L, which is the DOS of the last prescription. That happens when the study period ends before the DOS of the last prescription are used. Therefore, Borah et al. truncated the exceeding DOS to avoid overestimating adherence [2]. In the case of variable follow-ups, the follow-up either ends with the last prescription plus DOS_L, when all DOS are used, or at the date of the last prescription. The former was

usually performed, whereas the latter was used by Grijalva et al., who excluded the exceeding DOS_L from the MPR calculation according to [12]:

$$MPR = \frac{\sum_{t=0}^T \text{DOS} - \text{DOS}_L}{T},$$

where T indicates the whole study period.

All MPRs can get larger than 1 if more prescriptions are filled than are needed. In such cases, Tkacz et al. normalized the MPR to 1 [22]. This is not necessary with the PDC because it avoids double counting the days where daily doses are on hand [13]. In five studies, PDCs are reported [13, 22, 23, 28, 29]. Thereof, two studies lacked a precise definition of the PDC calculation. Thus, their methods are not described here [22, 29]. Li et al. [13] gave a very precise description of the PDC. Their method is shown in Figs. 2 and 3. In the case of the subcutaneous (s.c.) application of TNF inhibitors by the patient, the provided syringes are storable (Fig. 2). Therefore, DOS of prescription V_1 exceeding the date of the next prescription V_2 can be added to the DOS of prescription V_2 . In contrast, IFX is administered in a clinical setting. Therefore, DOS exceeding the next prescription are not storable (Fig. 3) and premature administration of i.v. drugs does not extend the next expected prescription interval. That is why Li et al. [13] used different procedures for calculating the days with drugs on hand for s.c. and i.v. TNF inhibitors, respectively. Because of the storability of s.c. drugs, the remaining DOS from a previous prescription are added to the following DOS, plus the day of the new prescription, for which adherence can be assumed (Fig. 2). DOS of i.v. and s.c. drugs exceeding the end of the study are excluded. The remaining gap equals the days without medication on hand

Table 3 Criteria used to describe persistence of medication

Time frame	Switch allowed?		
	Yes	No	Not specified
Not specified		Harrison et al. [3] ^a Sangiorgi et al. [10]	Tang et al. [47]
30 days + DOS		Borah et al. [2] Yazici et al. [15] ^b Thagarajan et al. [51]	
31 days + DOS ^c	Curkendall et al. [21]		
45 days		Wu et al. [24]	
45 days + DOS		Bonafede et al. [49] ^d Fisher et al. [39]	Howe et al. [14]
60 days + DOS		Zeidler et al. [4] Blume et al. [44] Joyce et al. [36] ^a Neubauer et al. [9] ^e	Wu et al. [34]
61 days + DOS ^c		Ogale et al. [17] ^f	
73 days		Bonafede et al. [23] ^g	
90 days		Johnston et al. [20]	Tkacz et al. [22] Tkacz et al. [31]
90 days + DOS		Grijalva et al. [12] Li et al. [13] ^h Zhang et al. [29] Tkacz et al. [31]	
90 days + usual dosing interval		Zhang et al. [29]	
14 weeks			Cho et al. [8]
180 days		Harnett et al. [19]	
110 % of expected dosing interval + DOS		Tkacz et al. [31]	

ADA adalimumab, DOS days of supply, ETN etanercept, IFX infliximab, s.c. subcutaneous

^a Switchers were excluded from the analysis

^b Method of DOS calculation is not explicitly given

^c The day of prescription is added to the DOS

^d DOS ETN = 7 days for a 50-mg syringe; DOS ADA = 14 days for a 40-mg syringe; DOS IFX = 56 days for one infusion

^e Subgroup analyses for switcher and non-switchers; sensitivity analyses with gaps of 30, 60, and 120 days

^f Sensitivity analysis for gaps of 180 days

^g For s.c. drugs, an overlay up to 14 days is added

^h Sensitivity analysis for gaps of 30, 60, and 120 days

[7]. Curtis et al. and Bonafede et al. used a similar technique, where they limited the added period in s.c. TNF treatment to a maximum of 14 days [23, 28]. Finally, they calculated the PDC for s.c. and i.v. drugs by dividing the days with medication on hand by the time of follow-up [13].

Another measure of adherence is the compliance ratio, used by Harley et al., as well as by Tkacz et al., for injections and infusions alike. It is the ratio between the

number of actual and expected prescriptions within a period [30, 31]. It can be larger than 1 if more prescriptions are filled than what was expected.

Although the reported measures of adherence are continuous, it is frequently reported as a binary variable [2, 13, 22, 23, 28–30]. To this end, a threshold for ratios, for example of 80 %, is specified, beyond which a patient is considered to be adherent [2, 13, 23, 25, 28–30]. In one study, adherence is not defined as a continuous measure,

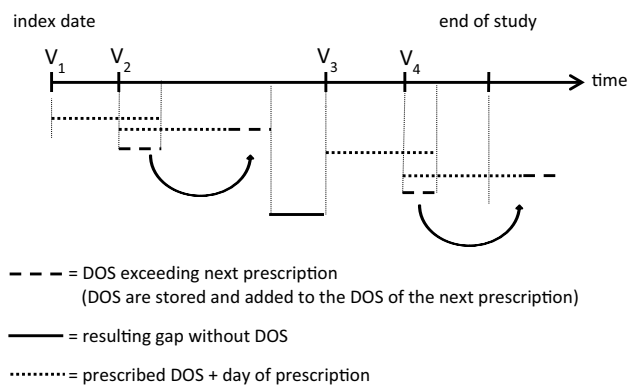


Fig. 2 Proportion of days covered according to Li et al. [13] for subcutaneous drugs. *DOS* days of supply

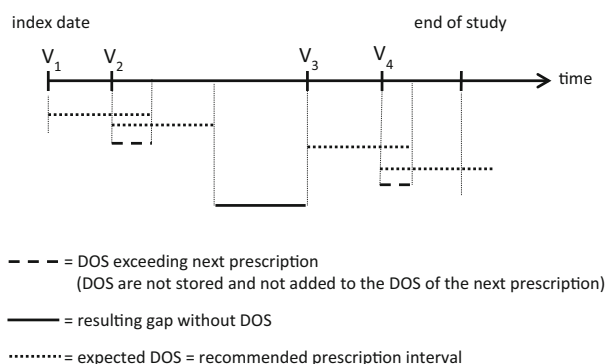


Fig. 3 Proportion of days covered according to Li et al. [13] for intravenous drugs. *DOS* days of supply

although the MPR and the PDC are reported. Instead, the authors defined a new prescription as adherent if it is filled within 21–38 days after the previous one [22]. Similarly, Curtis et al. defined i.v. therapy as adherent if the number of infusions at least equals the expectations [25–28].

Tkacz et al. also used other novel measures of adherence for infusions based on infusion gaps above expectations and on the number of infusions because DOS were not available for these agents [31]. They accumulated treatment gaps, which are defined as the difference between observed and expected infusion intervals. These gaps were categorized as those that are at least 20 % above expectation on those that do not increase expectation by any amount. They also identified variations in adherence by observing the occurrence of different predefined categories of gaps within a treatment period. Another measure of adherence was defined as the number of infusions in 1 year with gaps of at least 10 % above the expected interval [31].

3.3 Changes in Dosage

Changes of prescribed doses can lead to decreases or increases in daily dose. Sometimes, changes exceeding or

falling below a certain threshold are required to define an increased or decreased dose. A dosage complying with a definition like that is also called dose escalation. In all studies considering dosage changes, dose escalations were examined. In all, six studies [11, 15, 30, 32–34] considered reductions and four [11, 15, 33, 34] investigated stable doses. One study, where reduced doses are calculated, is not included here because it was missing an explanation and definition of the term ‘reduced dose’ [29].

A dose has to be compared with a reference dose to decide whether the dose is changed. As a reference, the index dose, the recommended dose, or the previous prescribed dose was used. In the identified literature, usually the first dose after a recommended loading period or the first stable dose was defined as the maintenance dose [9, 10, 17, 35–40].

The dose that is compared with the reference dose usually is the mean daily or mean weekly dose. It is calculated by dividing the absolute prescription dose either by the DOS prescribed or by the prescription interval (see, for example [23, 39, 41, 42] and [10, 11]). In all other studies, the absolute prescription dose was used instead. All but one study used supplementary definitions for changed doses [40]. These definitions are based on the prescription interval or the number of prescriptions within an interval.

3.3.1 Last Prescription

The deviation between the last dose and its reference is used for i.v. and s.c. drugs. The variations within this category and the associated studies are shown in Table 4. As references, the index and the maintenance dose were used. The maintenance dose is employed for IFX-naïve patients because of the recommended loading period. However, with s.c. drugs without a loading period or with experienced IFX patients, the index dose was used [3, 36]. Nevertheless, three studies used the index dose for IFX-naïve patients as well [11, 30, 43]. In most cases, any change in the last dose compared with its reference was sufficient to define a changed dose. Harrison et al. as well as Blume et al. required an increase over 10 % for dose escalation [35, 44]. For IFX and GLM, an increase of the last dose compared with the index dose of at least 100 mg/application and 25 mg/week were required in four [25–28] and three studies, respectively [25, 26, 28].

3.3.2 Any Prescription

The definitions used for any dose compared with its reference over the follow-up are shown in Table 5. In such a way, the index, maintenance, recommended, or previous doses were used. These reference doses were applied to s.c.

Table 4 Criteria used for the definition of ‘last prescription’

Change in dose	Reference dose	
	Index dose	Maintenance dose
Any	Harley et al. [30] Berger et al. [32] Weycker et al. [11] Nair et al. [43] Harrison et al. [3] Huang et al. [41] Joyce et al. [36]	Joyce et al. [36]
10 %	Harrison et al. [3] ^a Blume et al. [44]	Harrison et al. [3] ^a
100 mg/application (IFX)	Curtis et al. [25] Curtis et al. [26] Oladapo et al. [27] Curtis et al. [28]	
25 mg/week (GLM)	Curtis et al. [25] Curtis et al. [26] Curtis et al. [28]	

GLM golimumab, IFX infliximab

^a In the case of IFX, the change in dose refers to the absolute prescribed dose, not to the mean daily dose between two prescriptions. To consider time, a reduction in the length of a prescription interval or an increased number of infusions is also defined as an increased dose according to Table 7

injections and infusions alike. In 19 records, any increase or decrease of a prescription was defined as a dosage change. In other studies, various minimum thresholds were defined. These thresholds ranged from 10 to 100 %. Furthermore, some methods require these changes in at least two consecutive observations [10, 17, 33, 44, 37].

In four studies, no reference for dosage analyses of ADA and ETN was used [25–28]. These studies are shown in Table 6. Here, a weekly prescription dose of at least 40 mg ADA or 100 mg ETN was sufficient for dose escalation.

As opposed to s.c. agents, daily doses are difficult to calculate with IFX, because for infusions, DOS are not given in the claims data and appropriate IFX dosage is dependent on the patient’s weight [16, 45]. Therefore, a supplementary definition of dose increase with IFX is often defined with reduced prescription intervals [35, 34, 39, 46] or an increased number of infusions within a certain period [17, 25–28, 38] as depicted in Table 7. Sometimes, this increase must be observed in at least two occasions [17, 38, 46]. For example, Curtis et al. considered a prescription quantity of more than 120 % of that which was expected as an increase in dose [25–28]. In other cases, reductions in the recommended infusions period of 8 weeks [45] to either fewer than 6 or fewer than 7 weeks was defined as an increase in dose [34, 46, 39].

Wu et al. are the only individuals who defined reduced doses within this class of methods [34]. They also applied a particularly complex method to patients who did not start with the recommended dose [34]. The authors defined a change in dosage in ADA and ETN therapies from the healthcare provider’s point of view. They assigned the mean doses of the treatment of naïve patients into four dosage categories. Mean doses were calculated differently according to the prescription gaps. If gaps were small or negative, the DOS given in the prescriptions were taken as the denominator. Otherwise, the prescription interval was used. Accordingly, the prescribed mean dose was used in the former case, whereas the real mean dose seemed more appropriate to the authors in the last case. The resulting dosage categories were applied to define a change in dose using the first stable dose as a reference. An increase or decrease in dose was defined as at least two switches to a higher or lower class, respectively. The first stable dose was defined as the second prescribed dose if the first and second doses were the same. If the second and third doses were equal, the third dose was defined as the first stable dose. Otherwise, the mean value of the first three prescribed doses was used. If fewer than three prescriptions were available, the index dose was used as the reference.

3.3.3 All Prescriptions

With this approach of calculating mean doses, all prescriptions within a certain period are taken into account (Table 8). The recommended, the index, or the maintenance dose is compared with the mean dose of all prescriptions of a specific period. If the index or maintenance dose is the reference, it was excluded from the calculation. Two exceptions are the studies of Zeidler et al. and Fisher et al. where the maintenance dose was included [4, 39]. Huang et al. determined the mean dose for each period between the index dose and every following prescription [41]. To identify a dose escalation, at least two of these mean values had to be greater than the index dose [41]. As in the previous methods, a certain threshold was defined in some studies to determine a changed dose.

4 Discussion

The objective of the present systematic review was to describe and assess methods in published dosage analyses of TNF inhibitor therapy of patients with RA based on claims data. The methods of the identified 45 studies of relevance were compared and grouped into switching, adherence, persistence, and dosage-change analyses.

In switching analyses, a certain time frame where switching must occur was rarely used (Table 2). It should

Table 5 Criteria used for the definition of ‘any prescription’

Change in dose	FRQ	Reference dose			
		Index dose	Maintenance dose	Recommended dose	Previous dose
Any change	1	Gu et al. [48] Harrison et al. [3] Huang et al. [41] Bolge et al. [40] Curtis et al. [25] ^a Curtis et al. [26] ^a Oladapo et al. [27] ^a Curtis et al. [28] ^a	Ollendorf et al. [46] ^a Bolge et al. [40] Fisher et al. [39] ^a	Blume et al. [44] Fisher et al. [39] Bonafede et al. [23]	Etemad et al. [42]
Any change	2		Gilbert et al. [38] ^a Wu et al. [34] ^a Ogale et al. [17] ^{a,b}		
Any change	Each fill	Yazici et al. [15]			
10 %	1	Harrison et al. [3] ^a Bonafede et al. [23] ^c			
20 %	2		Ollendorf et al. [33] ^b		
30 %	2	Blume et al. [44] ^b	Ollendorf et al. [33] ^b Chastek et al. [37] ^b Sangiorgi et al. [10] ^b	Chastek et al. [37] ^b	
33.33 %	1		Neubauer et al. [9]	Neubauer et al. [9]	
40 %	2		Ollendorf et al. [33] ^b		
100 %	2			Wu et al. [34]	
5 mg/week ETN	1				Etemad et al. [42]
To different class	2		Wu et al. [34] ^d		

ETN etanercept, FRQ frequency, IFX infliximab, i.v. intravenous, s.c. subcutaneous

^a In the case of IFX, the change in dose refers to the absolute prescribed dose, not to the mean daily dose between two prescriptions. To consider time, a reduction in the length of a prescription interval or an increased number of infusions is also defined as increased dose according to Table 7

^b The increased doses need to follow one another

^c After a first increased dose of s.c. drugs is found, it became the new reference dose. If the paid amount for i.v. drugs increased by 10 %, this was also defined as dose escalation

^d The reference dose is the first stable dose within the first three prescriptions

Table 6 Criteria used for the definition of ‘any prescription’

Change in absolute prescription dose	FRQ	No reference dose
≥40 mg/week (ADA)	1	Curtis et al. [25] Curtis et al. [26] Oladapo et al. [27] Curtis et al. [28]
≥100 mg/week (ETN)	1	Curtis et al. [25] Curtis et al. [26] Oladapo et al. [27] Curtis et al. [28]

ADA adalimumab, ETN etanercept, FRQ frequency

be noted that if a time frame is not used, persistency within treatment cannot be ensured. Furthermore, if the termination of the previous treatment is not verified, it is not possible to differentiate co-medication from switching.

For persistence analyses, the usefulness of a time frame should be also considered. With very small gaps, patients who are not 100 % adherent will be considered non-persistent. Given the widely accepted adherence level of 80 %, this assumption seems not to be plausible. However, very large gaps could overestimate persistence, if persistency is mixed with termination and restart of therapy. To our knowledge, there is no widely accepted standard for the length of the time gap in persistence analyses. Therefore, sensitivity analyses with varying prescription gaps may be useful.

When the MPR is used, analysts should bear in mind that the MPR in contrast to the PDC is a simple summation of DOS divided by the treatment period (Sect. 3.2.3). The PDC is slightly more complicated to calculate but its assumptions concerning the storability of different drugs seem to be more realistic (Figs. 2, 3). With the PDC, days

Table 7 Supplementary definition of dose escalation in case of IFX dosage analyses

Change in prescription interval or number of infusions	FRQ	Article
Changed prescription interval		
Any change from index to last prescription interval	1	Harrison et al. [3]
Prescription interval of <6 weeks	1	Fisher et al. [39]
Prescription interval of <7 weeks	1	Wu et al. [34]
	2	Ollendorf et al. [46]
Prescription interval of > 9 weeks (definition of decreased dose)	1	Wu et al. [34]
Changed number of infusions		
Increased number of infusions of >20 % compared with expectation	1	Curtis et al. [25] Curtis et al. [26] Oladapo et al. [27] Curtis et al. [28]
≥2 infusions within 7 weeks	2	Gilbert et al. [38] Ogale et al. [17]

FRQ frequency, IFX infliximab

Table 8 Criteria used for the definition of ‘all prescriptions’

Change	Dose of interest: mean dose calculated for the period	Reference dose		
		Index dose	Maintenance dose	Recommended dose
Any change	After reference dose to each subsequent prescription	Huang et al. [41] ^a Joyce et al. [36]		
	After reference dose to end of follow-up Of the entire follow-up		Joyce et al. [36]	Huang et al. [41] Joyce et al., 2014 [36]
10 %	Of the entire follow-up		Fisher et al., 2013 [39]	Blume et al. [44] Fisher et al. [39]
15 %	After reference dose to end of follow-up	Huang et al. [41]		
30 %	After reference dose to end of follow-up	Huang et al. [41] Blume et al. [44]	Chastek et al. [37]	
33.3 %	After reference dose to end of follow-up		Wu et al. [34]	
	Of the entire follow-up		Zeidler et al. [4]	Wu et al. [34] Zeidler et al. [4]
50 %	After reference dose to end of follow-up	Huang et al. [41]		

^a In comparison to the index dose, the mean weekly dose must be increased at least two times

with drugs on hand that exceed the next prescription are just carried over into the future and not into the gaps in the past. In contrast to the calculation of the MPR, all DOS within the follow-up period are taken into account. Therefore, DOS exceeding the next prescription can offset prescription gaps in the past as well as in the future. Hence, the MPR may overestimate persistence, as compared with PDC.

There is a wide variety of dosage change analyses. The calculation of ‘last prescription vs. reference’ may be one of the easiest, but it does not consider interim changes in doses. In contrast, ‘any dose vs. reference’ takes every

prescription into account. Therefore, it is a very sensitive method and could overestimate changes in dose, for example, when the increased prescription is an outlier or error in the claims data. Therefore, sensitivity analyses with different methods and varying thresholds could be conducted or, for definition of dose decrease or escalation, multiple dosage changes could be required [10, 34, 33, 38]. Because with ‘every dose vs. reference’ the overall prescription mean is compared, the influence of an outlier could be diminished. However, it should be noted that with exception of the method of Wu et al., where a new prescription mean after each prescription is calculated, the

course of the dosage over the treatment period cannot be identified [34].

As reference doses, observable prescription doses within therapy such as the index dose, maintenance dose, or the previous dose may be advisable if changes within therapy should be identified. If treatments should be compared with treatment recommendations, for example, for guideline evaluations, a suitable reference dose may be the recommended dose. The interpretation of the index dose depends on the definition on the patient's experience. If the study analyzes treatment-naïve patients, the index dose equals the initial dose, which is the first treatment dose. Otherwise, if experienced patients are analyzed or if no loading period is recommended, the index dose and maintenance dose could be the same. The loading period is the first period of the therapy where the maintenance level has not been reached.

Because of the high impact of dosage on costs and the impact of the virtue of therapy on adherence, persistence, and dose, dosage analyses are important for healthcare payers, healthcare providers, and patients alike. To facilitate further claims data-based research in this area, we present a comprehensive overview and a short discussion of current methods. Because we did not assess quality of methods quantitatively, further research in this area is needed.

The present study is limited to publications in the English or German languages. Furthermore, a detailed explanation of the methods used was not provided in every study. Hence, opportunities for comparison are restricted. Moreover, most studies are performed with US claims data. Owing to restrictions in available data, the methods reviewed in this study may not generalize to every country.

5 Conclusions

This systematic review identified a high variation of methods used in dosage analyses applied to claims data of TNF inhibitor treatment among patients with RA. Our information and suggestions may be helpful for choosing appropriate methods in future studies and greatly facilitate further dosage analyses. Additionally, the presented systematic comparison of methods demonstrates the need for standardized methodology concerning the design, conduct, analysis, and reporting of claims data studies in rheumatology. Evidence-based methodology is a prerequisite for cross-study comparisons and to reliably calculate the healthcare costs of TNF inhibitors in actual patients with RA.

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Compliance with Ethical Standards

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