World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i27.4344

World J Gastroenterol 2013 July 21; 19(27): 4344-4350
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Low rates of adherence for tumor necrosis factor-α inhibitors in Crohn's disease and rheumatoid arthritis: Results of a systematic review

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Received: December 24, 2012 Revised: February 12, 2013
Accepted: March 21, 2013
Published online: July 21, 2013

Abstract

AIM: To investigate adherence rates in tumor necrosis factor-α (TNF-α)-inhibitors in Crohn's disease (CD) and rheumatoid arthritis (RA) by systematic review of medical literature.

METHODS: A structured search of PubMed between 2001 and 2011 was conducted to identify publications that assessed treatment with TNF-α inhibitors providing data about adherence in CD and RA. Therapeutic agents of interest where adalimumab, infliximab and etanercept, since these are most commonly used for both diseases. Studies assessing only drug survival or continuation rates were excluded. Data describing adherence with TNF-α inhibitors were extracted for each selected study. Given the large variation between definitions of measurement of adherence, the definitions as used by the authors where used in our calculations. Data were tabulated and also presented descriptively. Sample size-weighted pooled proportions of patients adherent to therapy and their 95%CI were calculated. To compare adherence between infliximab, adalimumab and etanercept, the adherence rates where graphed alongside two axes. Possible determinants of adherence were extracted from the selected studies and tabulated using the presented OR.

RESULTS: Three studies on CD and three on RA were identified, involving a total of 8147 patients (953 CD and 7194 RA). We identified considerable variation in the definitions and methodologies of measuring adherence between studies. The calculated overall sample size-weighted pooled proportion for adherence to TNF-α inhibitors in CD was 70% (95%CI: 67%-73%) and 59% in RA (95%CI: 58%-60%). In CD the adherence rate for infliximab (72%) was highercompared to adalimumab (55%), with a relative risk of 1.61 (95%CI: 1.27-2.03), whereas in RA adherence for adalimumab (67%) was higher compared to both infliximab (48%) and etanercept (59%), with a relative risk of 1.41 (95%CI: 1.3-1.52) and 1.13 (95%CI: 1.10-1.18) respectively. In comparative studies in RA adherence to infliximab was better than etanercept and etanercept did better than adalimumab. In three studies, the most consistent factor associated with lower adherence was female gender. Results for age, immunomodulator use and prior TNF-α inhibitors use were conflicting.

CONCLUSION: One-third of both CD and RA patients treated with TNF-α inhibitors are non-adherent. Female gender was consistently identified as a negative determinant of adherence.

Key words: Adherence; Tumor necrosis factor-α inhibitors; Systematic review; Crohn's disease; Rheumatoid arthritis

Core tip: This study assessed adherence with tumor ne-

crosis factor-α (TNF-α) inhibitors in Crohn's disease (CD) and rheumatoid arthritis (RA) by systematic review. We found only two-third of the patients with CD and RA receiving TNF-α inhibitors adherent to therapy. Definitions of measurement of adherence varied widely between studies and there is no clarity on what levels of adherence are required for optimal results of therapy. Future research on adherence should focus on therapy outcome, by using uniform definitions of adherence.

Fidder HH, Singendonk MMJ, van der Have M, Oldenburg B, van Oijen MGH. Low rates of adherence for tumor necrosis factor-α inhibitors in Crohn's disease and rheumatoid arthritis: Results of a systematic review. *World J Gastroenterol* 2013; 19(27): 4344-4350 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i27/4344.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i27.4344

INTRODUCTION

Crohn's disease (CD) and rheumatoid arthritis (RA) are chronic inflammatory conditions characterized by episodes of remission and flare-ups that have a major impact on the patient's physical, emotional and social well-being. The management of these diseases has been profoundly modified by the introduction of tumor necrosis factor-α (TNF-α) inhibitors, *i.e.*, infliximab, adalimumab and etanercept (only in RA), and these agents have become an integral part of the therapeutic arsenal. In RA TNF-α inhibitors have shown to rapidly improve symptoms, retard radiographic disease progression and improve functional status and health-related quality of life[1]. Also in CD TNF-α inhibitors are highly efficacious for induction and maintenance therapy and reduce rates of hospitalization and surgery[2].

Clinical effectiveness of TNF-α inhibitors is dependent on adequate adherence, and failure to stick to the prescribed drug regimen contributes to failure of treatment and disease recurrence. For both RA and CD, good adherence is associated with more effective treatment, including limited loss of response[3,4]. Fernández-Nebro *et al*[4] reported that in CD the probability of premature failure of TNF-α inhibitors was 61% less in patients with good adherence.

For patients with inflammatory bowel disease, reported non-adherence rates for oral medication range in most studies between 30%-45%[5]. Low adherence has an impact on healthcare budgets by increasing number of treatment failures, subsequent diagnostic procedures and unnecessary change of therapy. A Cochrane review on adherence concluded that improving medicine intake may have a far greater impact on clinical outcomes than an improvement in treatments[6]. In line with this statement Kane *et al*[7] pointed out that all-cause and CD-related medical costs were 81% and 94% higher, respectively, for non-adherent patients in comparison to adherent patients.

Although it has been 15 years since TNF-α inhibitors were introduced for the treatment of CD and RA, our understanding of patient's compliance to TNF-α inhibitors is minimal and reported rates of adherence vary widely, depending on the definition of adherence. In order to assess the adherence rates for TNF-α inhibitors in CD and RA, we systematically reviewed literature and performed meta-analysis.

MATERIALS AND METHODS

We conducted a structured search of PubMed to identify potentially relevant English-language publications that assessed adherence to TNF-α inhibitors in CD. In our search strategy, the following keywords and search strings were used: (infliximab OR Remicade OR adalimumab OR Humira OR etanercept OR Enbrel OR anti-TNF OR biological) AND Crohn AND (adherence OR compliance). In the same way, we conducted a search of PubMed to identify potentially relevant publications that assessed adherence with TNF-α inhibitors in RA, thereby substituting the search term "Crohn" for "RA". During the whole process the exact reporting guidelines as described in the PRISMA statement (www.prisma-statement.org) were followed.

Two investigators (Fidder HH and Singendonk MMJ) independently reviewed identified titles and abstracts of all citations in the literature search results. Potentially relevant studies were retrieved and the following predefined inclusion criteria were applied: (1) original research article; (2) adult patients; (3) definition of adherence provided; (4) methodology of measurement of adherence described; and (5) data based on number of patients. From selected abstracts, full articles were retrieved, reviewed and included if they contained data regarding adherence to TNF-α inhibitors in CD or RA. Disagreements between reviewers were adjudicated by discussion and consensus with a third-party arbiter (MvO).

The following information was extracted for each selected study: TNF-α inhibitors used, study design, sample size, definition of adherence measurement and the levels of adherence reported. We also sought for determinants of adherence in included studies, and tabulated the following factors of interest by using the presented OR: gender, age, duration of disease and therapy, prior and concomitant therapy. The data obtained from the selected articles describing adherence with TNF-α inhibitors were tabulated and also presented descriptively.

Given the large variations in definitions and methodologies of measurement of adherence and patient samples of the studies included, we used the definitions of adherence used by the authors in order to calculate the sample size-weighted pooled proportions of patients that were adherent to therapy and to compare adherence rates between adalimumab, infliximab and etanercept. To portray these data for each therapeutic agent, we graphed them alongside two axes; adherence rate re-

Table 1 Characteristics of included studies on Crohn's disease and rheumatoid arthriti

	Number of patients	Anti-TNF treatment	Definition of adherence	Adherence
Crohn's disease				
Kane *et al*[7]	571	Infliximab	≥ 7 infusions in first year of treatment	66%
Billioud *et al*[17]	108	Adalimumab	Neither delaying nor missing > 1 injection in 3 mo	55%
Kane *et al*[18]	274	Infliximab	No "No show" designation during study period	85%
Rheumatoid arthritis				
Borah *et al*[19]	2537	Etanercept	Medication possession ratio ≥ 0.80	71%
	1292	Adalimumab		67%
Harley *et al*[20]	853	Etanercept	Medication possession ratio ≥ 0.80	68%
	141	Infliximab		81%
Li *et al*[21]	1359	Etanercept	Proportion of days covered ≥ 0.80	32%
	1012	Infliximab		43%

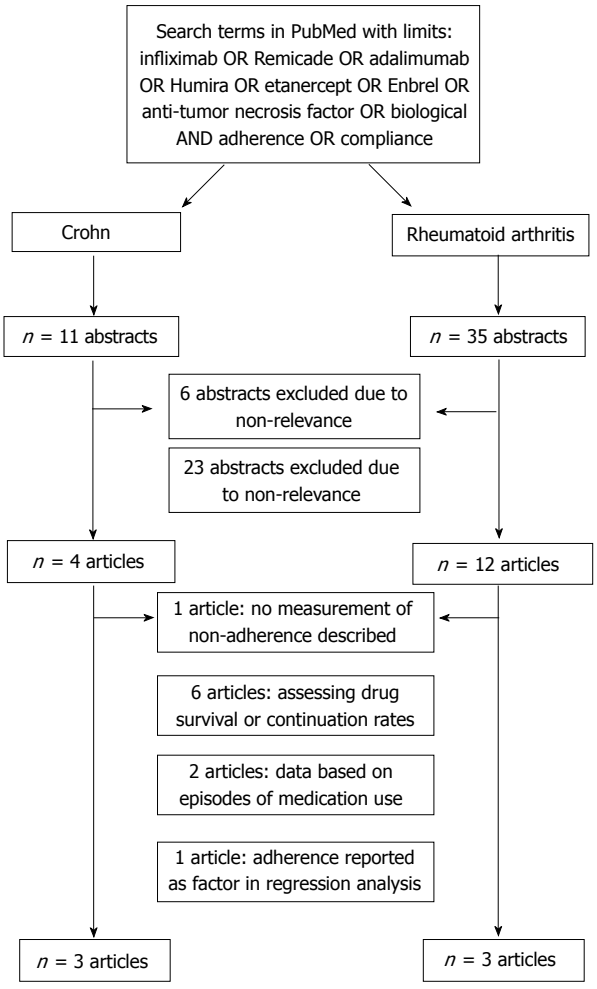

Figure 1 Results of literature search.

ported by the selected study for each agent and number of patients included.

RESULTS

Literature search

The search identified 11 studies regarding CD and 35 regarding RA, of which respectively 7 and 32 articles were excluded in two selection procedures. The main reason for exclusion of studies on CD was the absence of data on adherence or compliance (Figure 1)[8]. Exclusion of studies on RA was mainly based on the fact that these studies assessed drug survival or continuation rates only, but not compliance and/or adherence[4,9-13]. Three other studies were excluded: two studies based their data on episodes of medication use instead of number of patients[14,15] and one study only reported adherence as a factor in regression analysis[16]. Six articles that met our inclusion criteria remained, three on CD[7,17,18] and three on RA[19-21]. Characteristics of included studies are shown in Table 1.

CD

Two out of three studies on CD reported on adherence to infliximab[7,18] and one on adalimumab[17]. There were no comparative studies. We identified considerable variation in the definitions and methodologies of measuring adherence between studies. The adherence rate for all TNF-α inhibitors as calculated by the sample size-weighted pooled proportion was 70% (95%CI: 67%-73%). For adalimumab, the reported adherence rate was 55%[17] and for infliximab the reported rates were 66%[7] and 85%[18] (Table 1). Adherence to adalimumab (55%) was statistically significantly lower than infliximab (72%) therapy, with a relative risk of 0.76 (95%CI: 0.64-0.91) (Figure 2)[7,17,18].

RA

For RA we only found comparative studies: two of the included studies assessed adherence to both etanercept and infliximab[20,21] and one study compared etanercept with adalimumab[21]. In RA, measurement of adherence was based on medication possession ratios in two studies and one study measured adherence as the proportion of days covered (PDC). Medication possession rate (MPR) is defined as the sum of days supply for all fills in period divided by the number of days in a period. PDC is the number of days in a period covered by medication divided by the days in a period. In all studies patients were considered adherent if MPR or PDC was ≥ 0.8.

Reported adherence rates ranged from 32% to 81% (Table 1)[19-21]. The overall adherence rate was 59% (95%CI: 58%-60%), as calculated by the sample size-weighted pooled proportion. In the two studies compar-

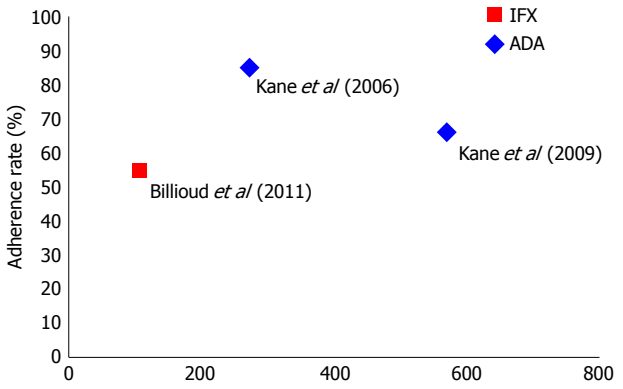

Figure 2 Adherence rates reported by the included studies on Crohn's disease for infliximab and adalimumab. The vertical axis rank-orders the therapeutic agents by the adherence rates and the horizontal axis by number of patients included. IFX: Infliximab; ADA: Adalimumab.

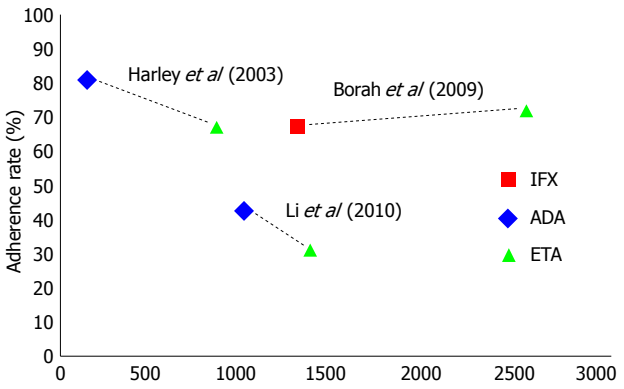

Figure 3 Adherence rates reported by the included studies on rheumatoid arthritis for infliximab, adalimumab and etanercept. The vertical axis rank-orders the therapeutic agents by the adherence rates and the horizontal axis by number of patients included. IFX: Infliximab; ADA: Adalimumab; ETA: Etanercept.

ing infliximab to etanercept adherence to infliximab was consistently higher (Figure 3)[20,21]. In the study comparing etanercept to adalimumab, patients using etanercept were slightly more adherent than adalimumab users[19]. After pooling the published adherence rates, we found the highest adherence rate for adalimumab (67%) compared to both infliximab (48%) and etanercept (59%), with a relative risk of 1.41 (95%CI: 1.3-1.52) and 1.13 (95%CI: 1.10-1.18) respectively.

Predictors

Five studies have formally explored possible predictors of (non)-adherence to TNF-α inhibitors (Table 2)[7,19-21]. The most consistent factor associated with lower adherence (reported by three studies) was female gender[7,20,21]. Increasing duration of therapy was reported as a factor negatively associated with adherence and duration of disease as factor associated with better adherence[7,18]. Results for age, immunomodulator use and prior TNF-α inhibitors use were conflicting[7,19].

DISCUSSION

We systematically reviewed adherence rates to TNF-α inhibitors in CD and RA. Although literature on adherence rates to TNF-α inhibitors in other rheumatological diseases exists, we did not assess adherence for these diseases given the relatively small patient numbers. Given the central position of TNF-α inhibitors in the management of CD and RA and the importance of adherence for effective treatment, the total number of six studies that adequately assessed adherence to anti-TNF therapy was surprisingly low. Our analysis of the included studies on CD and RA has three key findings. First, we found that adherence to TNF-α inhibitors in CD and RA is low, with only two-thirds of the patients being adherent to therapy. Second, adherence rates for adalimumab were lower compared to infliximab in CD. Last, we found that female gender was consistently associated with non-adherence to TNF-α inhibitors.

Our findings of rather low adherence to TNF-α inhibitors are in line with figures reported for adherence to oral medication in inflammatory bowel disease, that range between 28% and 93% of patients adherent to prescribed therapy[5,22,23]. In a comparative cohort study mesalazine and azathioprine were associated with the lowest compliance[24]. In RA the adherence rates for TNF-α inhibitors has been reported between 30% and 80%, depending on definitions used[25]. The low adherence to TNF-α inhibitors are especially worrisome since long treatment intervals are associated with infusion reactions and loss of response as result of increased antibody formation against TNF-α inhibitors[26-28]. Moreover, non-adherence in adalimumab treated patients predicts higher hospitalization rates and increased medical service costs[7]. Adherence to continuous maintenance treatment with TNF-α inhibitors is important for the efficacy of treatment.

Although the different routes and schedules of administration of TNF-α inhibitors and the different measures of adherence across studies may impede a direct comparison, we found lower adherence rates with adalimumab and etanercept. In RA, pooling the adherence rates gave higher adherence for adalimumab over infliximab but all comparative studies reported higher adherence rates for infliximab as well. Differences in patient numbers between studies and a difference between the number of studies used for calculating the pooled adherence rates for the single treatment modalities are underlying this conflicting finding. In addition, Li *et al*[21] assesses adherence rates with etanercept and infliximab by using the PDC, which is a more conservative estimate for adherence compared to the MPR. Discrepant adherence between treatment options may be explained by a number of reasons including dosing frequency and route of administration. Etanercept and adalimumab are self-administered subcutaneously, whereas infliximab is administered intravenously, by a healthcare professional in a clinical setting. As patients need to visit infusion sites, adherence is more controllable in favor of infliximab. Indeed, in the two comparative studies between infliximab and etanercept[20,21], higher adherence was found for the intravenously administered infliximab. In the study of

Table 2 Determinants of adherence in Crohn's disease and rheumatoid arthritis

	Studies on Crohn's disease			Studies on rheumatoid arthritis	
	Kane *et al*[7]	Billioud *et al*[17]	Kane *et al*[18]	Borah *et al*[19]	Li *et al*[21]
Female gender	OR < 1		OR < 1; $P < 0.05$		OR < 1
Increasing age		OR < 1			OR > 1
Immunomodulator use	OR > 1		OR < 1		OR > 1; $P < 0.05$[1]
Prior biologic use	OR < 1; $P < 0.05$			OR > 1; $P < 0.05$	
Increasing duration of therapy			OR < 1; $P < 0.05$		
Increasing disease duration		OR > 1; $P < 0.05$			

[1]Significant at $P < 0.05$ for age 55-64 years (OR = 1.49).

Borah *et al*[19] adherence of etanercept - which is injected once or twice a week - was slightly higher than adalimumab, which is mostly self-administered using a bi-weekly schedule. But still, even for the more controllable intravenously administered modalities, adherence rates are well below 100%.

In order to improve adherence, it is essential to identify and understand risk factors for non-adherence. Although several factors were reported as determinants of adherence by the reviewed studies, we did not find any of these factors consistently associated with non-adherence, with the exception of female gender. This is in contrast with a previous study on oral therapies in inflammatory bowel disease that identified female gender as a positive determinant of adherence[29]. Also in other fields of medicine attempts to identify clinical, demographic and treatment factors that consistently predict adherence have proven quite disappointing[6]. Jackson *et al*[5] who systematically reviewed factors associated with non-adherence to oral medication specifically for inflammatory bowel disease pointed out that that simple factors such as demographics or treatment regimens could not reliably predict adherence. Far more important determinants were psychological distress, patients' beliefs about therapy, and doctor-patient interactions[5]. For the clinician, it is essential to be aware of the importance of psychological factors in non-adherence and that significant improvement in terms of adherence may be achieved by fine-tuning doctor-patient communication and addressing patients' individual beliefs about disease and medications.

Our study has several strengths and limitations. We provided a detailed and systematic review of published literature and studied adherence rates on both CD and RA with TNF-α inhibitors. Koncz *et al*[30] reviewed compliance and persistence for TNF-α inhibitors only in RA patients. Contrary to this review we included only studies that assessed adherence rates based on number of patients included and reported individual adherence results. Furthermore, we identified potential predictors of adherence. In the evaluation of potential predictors of adherence, we had no access to original research data and therefore we were dependent on the analyses performed by others and could not perform an individual patient data meta-analysis. The major drawback of this approach is the lack of agreement in terminology and methodologies for measurement of therapy behaviour, making the results of studies assessing this issue difficult to interpret and compare. Compliance, persistence and adherence are definitions used for assessing this. The medication possession ratios of infliximab, etanercept and adalimumab ranged between 63% and 90% and PDC around 40%. The PDC provides a more conservative estimate of adherence compared to MPR when patients are switching drugs or using dual-therapy in a class. The differences between these terms have been defined in a report for the National Institute for Health Research by Mikkelsen *et al*[31] Compliance can be defined as "the extent to which the patients" behaviour matches the prescriber's recommendations' quantified as "a percentage of number of doses taken or therapy days available in relation to a fixed period of time". Persistence refers to how long the patient takes the medicine for and is therefore measured by units of time. Adherence covers both these aspects of medication taking behaviour. Although these definitions seem clear, methodologies of measurement vary and therefore hinder comparability of findings. These differences in measurement of adherence cannot be shrugged aside, but at this stage, based on currently available literature, we provided more insight in the TNF-α therapy behaviour of patients with CD and RA. Despite the mentioned limitations, it is still clear that adherence with TNF-α therapy is low for all different modalities. However, there is no clarity on what levels of adherence are required for optimal results of therapy yet and these levels might vary depending on disease activity and localization. Therefore, in the future adherence should be assessed in combination with therapy outcome in order to determine optimal treatment schedules by using uniform definitions of compliance, adherence and persistence.

In conclusion, through systematic review we found that only two-third of the patients with CD and RA receiving TNF-α inhibitors were adherent to therapy. Developing methods that properly assess medication adherence could provide tools for improvement of therapy outcome. Although female gender was identified as a negative determinant of adherence, one should be aware that mechanisms underlying adherence are complicated and probably not determined by simple patient's and treatment characteristics.

COMMENTS

Background

Crohn's disease (CD) and rheumatoid arthritis (RA) are chronic inflammatory conditions characterized by episodes of remission and flare-ups that have a major impact on the patient's physical, emotional and social well-being. The management of these diseases has been profoundly modified by the introduction of tumor necrosis factor-α (TNF-α) inhibitors.

Research frontiers

Clinical effectiveness of TNF-α inhibitors is dependent on adequate adherence, and failure to stick to the prescribed drug regimen contributes to failure of treatment and disease recurrence. For both RA and CD, good adherence is associated with more effective treatment, including limited loss of response.

Innovations and breakthroughs

The analysis of the included studies on CD and RA has three key findings. First, the authors found that adherence to TNF-α inhibitors in CD and RA is low, with only two-thirds of the patients being adherent to therapy. Second, adherence rates for adalimumab were lower compared to infliximab in CD. Last, they found that female gender was consistently associated with non-adherence to TNF-α inhibitors.

Applications

The authors found that only two-third of the patients with CD and RA receiving TNF-α inhibitors were adherent to therapy. Developing methods that properly assess medication adherence could provide tools for improvement of therapy outcome.

Peer review

This article investigated adherence rates inTNF-α-inhibitors in CD and RA by systematic review of medical literature, and is informative and well-presented.

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ISSN 1007-9327

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