

Adherence to Anti-TNF Therapy in Inflammatory Bowel Diseases: A Systematic Review

Anthony Lopez, MD,* Vincent Billioud, MD,* Carina Peyrin-Biroulet, MD,[†] and Laurent Peyrin-Biroulet, MD, PhD*

Background: Nonadherence to medications may affect disease outcomes. The aim of this article was to review methods of assessment, prevalence, and predictors of nonadherence to anti-tumor necrosis factor therapy in inflammatory bowel diseases (IBD).

Methods: Studies were identified through the electronic database of MEDLINE (up to January 2012) and the annual meetings of Digestive Disease Week, the American College of Gastroenterology, the United European Gastroenterology Week, and the European Crohn's and Colitis Organization.

Results: Among 1783 citations identified, 13 studies evaluated adherence to biologics in IBD. Several methods were used to assess adherence to anti-tumor necrosis factor, including the medication possession ratio, the medication refill adherence, and the Morisky Medication Adherence Scale 8. Pooled adherence to anti-tumor necrosis factor therapy was 82.6%. Pooled adherence was 83.1% in adalimumab and 70.7% in infliximab-treated patients. Female gender, smoking, constraints related to treatment, anxiety, and moodiness were associated with nonadherence to both infliximab and adalimumab. Concomitant immunomodulator use and time since first infusion more than 18 weeks were predictors for nonadherence to infliximab. Regimen of 40 mg every other week, syringe use (versus pen), internal medicine center prescription (versus gastroenterology center prescription), retail pharmacy (versus speciality pharmacy) and new user (versus previous user) were predictors for adalimumab nonadherence.

Conclusions: More than three-quarters of patients with IBD adhere to biologics. Predictors of nonadherence include female gender, smoking, constraints related to treatment, anxiety, and moodiness. These data could be used to develop intervention studies aimed at improving adherence to biologics in IBD.

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Key Words: anti-TNF, adherence, inflammatory bowel disease

An increased proportion of patients suffering from inflammatory bowel diseases (IBD) are receiving anti-tumor necrosis factor (TNF) agents. In a French referral center, 60% of patients with Crohn's disease (CD) received at least 1 anti-TNF agent in the era of biologics.¹ In the same referral center during the same period, the probability of receiving infliximab at 5 years from the time of diagnosis was 29% in patients with ulcerative colitis (UC).²

Adherence to treatment is recognized as a major therapeutic goal in chronic disorders, including diabetes,³ hypertension,⁴ or AIDS.⁵ However, adherence rates to long-term therapies seem low, with an average rate of 50%.⁶ Nonadherence with medication increases the risk of clinical relapse among patients with quiescent UC.⁷ Poor adherence may undermine the potential therapeutic

benefits of biologics by contributing to treatment failure⁸ and increasing the risk of developing immunogenicity to anti-TNF agents. Nonadherence has also been associated with increased health care costs.^{9,10}

Numerous methods have been developed to assess adherence to oral medications, including patient surveys, pill counts, and prescription claims.^{11,12} In IBD, several adherence scales have been used to assess drug adherence, such as the medication adherence reporting scale and the Modified Morisky Adherence Scale 8.¹³ However, no validated scale or definitions of nonadherence have been validated for biological therapies requiring scheduled subcutaneous or intravenous injection. The aims of this article were to review (1) the methods used to measure adherence, (2) the rates of adherence, and (3) the predictors of nonadherence in patients with IBD receiving infliximab or adalimumab.

METHODS

A literature search was conducted to identify studies that measured rates of adherence to biological treatments in patients with IBD in clinical practice. We conducted a computerized search of English language publications listed in the electronic databases of MEDLINE (source: PubMed 1990 to January 2012). Studies were identified using the following search terms: "Patient compliance" and "Medication adherence" as medical subject headings as

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From the *Inserm U954 and Department of Hepato-Gastroenterology, University Hospital of Nancy-Brabois, Vandoeuvre-lès-Nancy, France; and [†]Unité de coordination de tabacologie, Service de pneumologie, Hôpital de Brabois, Allée du Morvan, Vandoeuvre-lès-Nancy, France.

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Reprints: Laurent Peyrin-Biroulet, MD, PhD, Department of Hepato-Gastroenterology, University Hospital of Nancy-Brabois, Allée du Morvan, 54511 Vandoeuvre-lès-Nancy, France (e-mail: peyrinbiroulet@gmail.com).

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well as adherence, compliance, persistence and discontinuation as free text terms. These were combined with the set operator AND with studies identified with the search term “Tumor Necrosis Factor-alpha/antagonists and inhibitors” as medical subject headings as well as anti-TNF, infliximab, adalimumab and certolizumab as word text terms. Manual searches of reference lists from potentially relevant articles were used to identify any additional studies that may have been missed using the electronic search. We also hand-searched abstracts from the annual meetings of Digestive Disease Week, the American College of Gastroenterology, the European Crohn’s and Colitis Organization and the United European Gastroenterology Week between 2008 and 2011.

We performed a manual selection of studies that satisfied the following inclusion criteria: (1) observational studies, (2) enrolment of patients with IBD treated with any biologics and (3) available data about adherence or compliance. Medication adherence refers to the act of conforming to the recommendations made by the provider with respect to timing, dosage, and frequency of medication taking.^{14–16} Studies providing persistence or discontinuation rates only were excluded from this systematic review.

Eligible articles were reviewed in a blind manner by 2 different investigators (A.L. and V.B.), and the results of the primary research studies were abstracted onto specially designed data extraction forms. Agreement between investigators was >95% and disagreement in data extraction was resolved by consensus between the 3 investigators (A.L., V.B., L.P.B.).

RESULTS

Literature Search Results

Initial search of online databases yielded 1783 papers and was supplemented with conference abstracts. A total of 13 studies

were included in this review: 9 full text articles^{10,17–24} and 4 abstracts (Fig. 1).^{25–28}

Most of studies (62%) were retrospective^{10,18,20,22–24,26,27} and 5 of them (38%) were prospective.^{17,19,21,25,28} Five studies included both patients with CD and UC.^{19,21,25,26,28} Seven studies (54%) included exclusively patients with CD^{10,17,20,22–24,27} and only 1 study included exclusively patients with UC.¹⁸ One study focused on pediatric patients with IBD.²³ Infliximab and adalimumab adherence was evaluated in 5 studies^{10,18,19,23,24} and 3 studies,^{17,20,22} respectively, and the adherence to both biologics were evaluated in 5 articles.^{21,25–28} We failed to find any study evaluating certolizumab adherence in IBD. The main characteristics of the studies included are summarized in Table 1.

Adherence Assessment

Most of studies used pharmacy refill data (46%).^{18,20,22,24,27,28} Other sources were medical claims,^{18,26} registry,^{19,24} outpatient specialist visits,^{17,26} mailed questionnaire,^{19,21} insurance claims,^{10,23} self-reported surveys,^{25,28} and administrative data.²⁴

There is heterogeneity in the definition of adherence (Table 2). The medication possession ratio using a threshold of 80% was the most common method (38%).^{18,19,21,27,28} Other definitions were “at least a missed injection,”^{17,24} “<7 infusions during the first year of treatment,”^{10,23} “1 missed or postponed infusion,”²⁶ “at least 1 delayed injection,”²⁵ “no refill prescription at least once per year,”²⁰ and the utilization of medication refill adherence, without any threshold to distinguish nonadherent from adherent patients.²⁷

Adherence Rates

Studies included in the analysis evaluated a total of 93,998 patients from whom 77,684 were adherent to anti-TNF therapy.

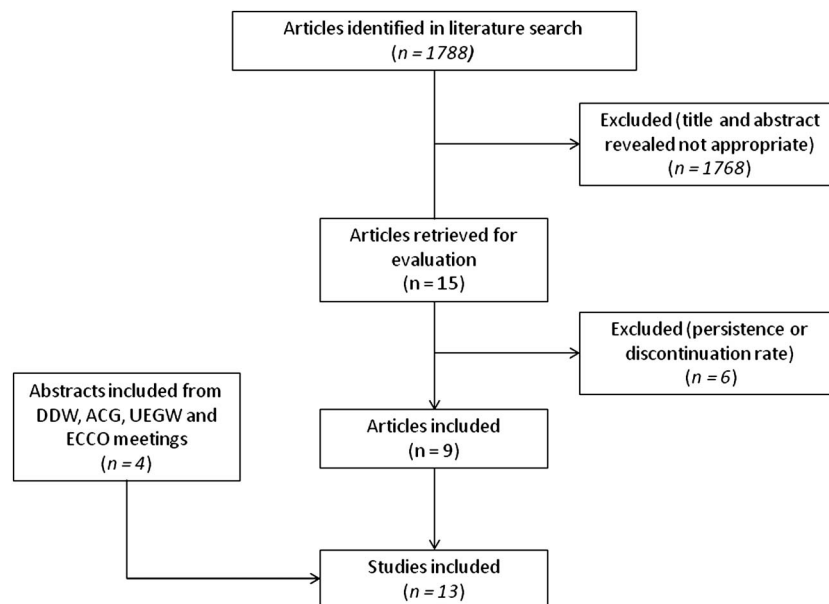


FIGURE 1. Flow chart of studies identified in the systematic review. Articles identified in literature search (n = 1783).

TABLE 1. Characteristics of the Studies Included in the Systematic Review

Study	Study Design	Disease Type	Study Population (n)	Study Duration (Weeks)	Biologic(s) Assessed
Kane et al, 2006	Retrospective	CD	274	68	Infliximab
Billioud et al, 2011	Prospective multicenter university-based cohort	CD	108	92	Adalimumab
Carter et al, 2011	Retrospective	UC	354	26	Infliximab
Kitney et al, 2009	Prospective unicenter university-based cohort	IBD	12	12	Infliximab
Carter et al, 2011	Retrospective	CD	638	104	Infliximab
Kane et al, 2009	Retrospective	CD	571	52	Infliximab
Nahon et al, 2011	Prospective	IBD	321	4	Infliximab/adalimumab
Duncan et al, 2011	Retrospective multicenter university-based cohort	IBD	106	52	Infliximab/adalimumab
Liu et al, 2011	Retrospective	CD	1083	64	Adalimumab
Kane et al, 2011	Prospective multicenter university-based cohort	IBD	26	36	Infliximab/adalimumab
Angelucci et al, 2011	Prospective unicenter	IBD	40	NA	Infliximab/adalimumab
Liu et al, 2010	Retrospective	CD, RA, PR, AS	86,079	48	Adalimumab
Mahic et al, 2011	Retrospective	CD, RA, psoriasis	4386	52	Adalimumab

PR, psoriatic arthritis; AS, ankylosing spondylitis; RA, rheumatoid arthritis; NA, not available.

The pooled adherence rate to biologics in patients with IBD was 82.6%, ranging from 36.8% to 96% (Table 2).

The pooled adherence rate was 83.1% (76,166/91,698) for adalimumab and 70.7% (1399/1979) for infliximab. Regarding disease type, the overall pooled adherence rates were 71.4% (2164/3030) and 52.7% (262/497) in patients with CD and UC, respectively. In patients with CD, the pooled adherence rate was 74.4% (263/1490) for infliximab and 85.2% for adalimumab (92/108). In patients with UC, the pooled adherence rate was 57.4% (206/359) for infliximab. Among pediatric patients with IBD, adherence rate to infliximab was 79.8% (10/12), with no significant differences between UC and CD.

Predictors of Nonadherence

Seven studies (54%) evaluated predictors for nonadherence.^{17,19–22,24,27} The most reliable predictor for nonadherence was female gender, identified in 4 studies.^{19,22,24,27} Other predictors for both adalimumab and infliximab nonadherence were smoking, constraints related to treatment, anxiety, and moodiness.²¹ Concomitant immunomodulator use and a time since the first infusion more than 18 weeks were identified in studies evaluating infliximab nonadherence.²⁴

For adalimumab therapy, regimen of 40 mg every other week,¹⁷ syringe use (versus pen),²⁷ internal medicine center prescription (versus gastroenterology center prescription),²⁷ retail pharmacy (versus speciality pharmacy),²² reimbursement by federal programs,²² copayment/payment amount,²² Hispanic/Black (versus White)²² and new user (versus previous user)²⁰ were associated with a poorer adherence.

DISCUSSION

This is the first systematic review assessing adherence to biologics in IBD. Overall, more than three-quarters of patients with IBD adhere to anti-TNF therapy. Previous studies mostly focused on adherence to oral therapies in IBD and described lower adherence rates. Adherence to oral 5-ASA agents ranged from 50% to 68%.^{29–31} For thiopurines, data are scarce and conflicting. Some studies used self-reported adherence surveys whereas others used metabolite concentration, with adherence rates ranging from 50% to 93%.^{32–34} These results are in line with nonadherence rates identified in other chronic diseases. About half of the patients who were prescribed an antihypertensive drug had stopped taking it within 1 year.³⁵ Better adherence to biologics could be explained by the route of administration (subcutaneously or intravenously of anti-TNF versus oral administration of 5-ASA and thiopurines) and the lower dosing frequency, whereas patients on oral therapy have to be adherent to a daily administered treatment and the need for regular monitoring and clinical visits. Furthermore, IBD patients under biologics suffer from more severe disease, which have been associated with a better adherence in IBD in a previous report.³⁶

We found that patients with CD seemed to be more adherent than patients with UC. We hypothesize that they are more adherent because their disease is often more disabling. Indeed, disease severity has been previously identified as a predictor of adherence in IBD.

A recent systematic review assessed adherence and persistence to biologics for rheumatoid arthritis, reporting adherence rates of 52% to 70% for adalimumab and 81% for infliximab.³⁷ Our

TABLE 2. Data Sources, Definition of Nonadherence, Adherence Rates, and Predictors of Nonadherence

Study	Anti-TNF Agent	Data Sources	Definition of Nonadherence	Adherent Patients, n (%)	Predictors of Nonadherence
Kane et al, 2006	IFX	Administrative data, pharmacy refill data, registry	At least a missed injection	263 (96)	Female, concomitant immunomodulator use, >18 weeks since first infusion
Billioud et al, 2011	ADA	Outpatient specialist visits	At least a missed injection	92 (85.2)	Regimen of 40 mg every other week
Carter et al, 2011	IFX	Medical and pharmacy refill data	MPR < 80%	202 (57.1)	NA
Kitney et al, 2009	IFX	Mailed questionnaire, IBD patient database	Taking < 80% of prescribed medication	10 (79.8)	Older age, longer disease duration, use of herbal medications, appointments in past year
Carter et al, 2011	IFX	Insurance claims	< 7 infusions during the first year of treatment	466 (73)	NA
Kane et al, 2009	IFX	Insurance claims	< 7 infusions during the first year of treatment	375 (657)	NA
Nahon et al, 2011	IFX/ADA	Mailed questionnaire	Taking < 80% of prescribed medication	118 (36.8)	Smoking, constraints related to treatment, anxiety, moodiness
Duncan et al, 2011	IFX/ADA	Medical claims and outpatient specialist visits	One missed or postponed infusion	IFX: 63 (76.8); ADA: 17 (70.8)	NA
Liu et al, 2011	ADA	Pharmacy refill data	MPR < 80%	790 (89)	Syringe use (versus pen), internal medicine center prescription (versus gastroenterology center prescription), female
Kane et al, 2011	IFX/ADA	Self-reported adherence survey and pharmacy refill data	MPR < 80%	13 (48)	NA
Angelucci et al, 2011	IFX/ADA	Self-reported adherence survey	At least a delayed injection	IFX: 12 (38.7); ADA: 8 (88.9)	NA
Liu et al, 2010	ADA	Pharmacy refill data	MRA	72,324 (84)	Retail pharmacy (vs speciality pharmacy), reimbursement by federal programs, copayment/payment amount, female, Hispanic/Black (versus White)
Mahic et al, 2011	ADA	Pharmacy refill data	No refill prescription at least once per year	2931 (67%)	New user (versus previous user), female, age <40 years and >59 years

IFX, infliximab; ADA, adalimumab; MPR, medication possession ratio; MRA, medication refill adherence; NA, not available.

systematic review showed a trend toward a higher adherence to adalimumab than to infliximab, showing that self-administration of adalimumab therapy does not impair anti-TNF adherence in patients with CD. Higher adherence rates to adalimumab may be partly explained by the fact that only patients with CD were treated with this biological agent, whereas infliximab was prescribed for patients with CD and UC. However, differences in methods and study design between studies do not allow a direct comparison between these 2 anti-TNF agents. Furthermore, only 13 studies were included and most of them were retrospective, whereas 4 were available only as an abstract. Finally, some studies included a mixed population (rheumatoid arthritis, psoriasis, and IBD), and no data were provided according to disease type.

Predictors identified in the present meta-analysis allow the identification of a target population who could benefit from interventions aimed at improving adherence in biologics-treated patients with IBD. Females, smokers, and patients suffering from concomitant psychiatric disorders are at increased risk of non-adherence. Other predictors seem to be more specific to anti-TNF agents, such as new users or patients treated for more than 18 weeks. We hypothesize that previous users are more adherent compared with new users because they could suffer from a more severe disease. Patients treated for more than 18 weeks are more likely to be in remission, so they could not feel necessary to continue their therapy. In line with previous reports, females were less adherent to anti-TNF therapy, probably because of additional

obligations, including balancing work and childcare. For Nahon et al,²¹ “constraints related to treatment” was a predictor of non-adherence. However, no clear definition was given by the authors; they hypothesized that patients referred to logistic constraints (work rhythms, etc.). For instance, the prescription of a pen formulation by a gastroenterologist and a retail pharmacy issue could also lead to increased adherence rates.

A wide range of tools have been used to assess adherence to anti-TNF therapy in IBD. Some of them have been validated for other drugs used in different chronic disorders, such as the medication possession ratio or the medication refill adherence.³⁸ Only 1 adherence scale has been validated in patients with IBD, the Morisky Medication Adherence Scale 8.¹³

Methods validated in other chronic disorders, such as electronic reminder device in hypertension or SMS in asthma, could be used in patients with IBD.^{39,40} Importantly, several studies demonstrated that nonadherence affects disease outcomes in patients with chronic conditions.^{3–5} Furthermore, drug adherence is associated with lower health care costs.^{9,10} Patients with UC who were persistent with their 5-ASA medications incurred 12.5% lower medical costs.⁹ Similarly, nonadherent patients with CD treated with infliximab are more likely to be hospitalized and their hospitalization costs are 115% greater compared with adherent patients.¹⁰ Relapse occurs in 61% of nonadherent patients with UC to 5-ASA compared with 11% of adherent patients.⁷ Volitional nonadherence is also associated with greater disease activity and poorer quality of life in pediatric patients with IBD.⁴¹ Therefore, improving adherence to anti-TNF agents may improve disease outcomes and should be a main therapeutic goal in clinical practice.

In conclusion, more than three-quarters of patients adhere to their biological treatment. Preventive measures and identification of population at risk to be nonadherent could improve treatment efficacy and disease outcome and decrease health care costs in IBD. Predictors for nonadherence to anti-TNF therapy in IBD could be used in future intervention studies.

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