Review

Adherence to biologic therapies and associated factors in rheumatoid arthritis, spondyloarthritis and psoriatic arthritis: a systematic literature review

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ABSTRACT

Objective. *To analyse the evidence on adherence to biologic therapies in rheumatoid arthris (RA), spondyloarthritis (SpA), and psoriatic arthritis (PsA).*

Methods. *Systematic review of studies retrieved by a sensitive search strategy in MEDLINE database (1961 through March 2012). To be selected, studies had to include patients with RA, SpA, or PsA, treatment with intravenous or subcutaneous biologic therapies, and had to report on measures of adherence. By design, only randomised controlled trials (RCT) or high quality cohort studies with a control group were selected.*

Results. *A total of 24 studies were included, of which 12 reported results from national or local biologic registers, 9 were retrospective studies, 2 prospective studies, and only one was an RCT. Patients included were mostly women with diagnosis of RA or SpA and, less frequently, PsA. There was a great variability in the definition of adherence, measurement methods, and associated factors analysed. In general, adherence to etanercept was superior to that of other biologics, by the measures utilised. The main predictive factors – age, sex, comorbidity, baseline clinical condition, previous or concomitant use of DMARDs, anti-TNF in monotherapy or in combination with MTX – produced diverse, even divergent results across studies.*

Conclusion. *There is a wide variability related to the adherence concept and its measurement, reflecting the complexity of the phenomenon. In order to draw more consistent conclusions about the relative value of predictive factors on adherence and persistence of biological therapy, larger controlled studies with better selection of variables and analysis of interactions are needed.*

Introduction

During the last decade, biologic therapy has been widely used in rheumatology for the treatment of different diseases such as rheumatoid arthritis (RA), spondyloarthritis (SpA) or psoriatic arthritis (PsA).

However, the potential benefits demonstrated by biologics in clinical trials may be undermined by poor adherence and early discontinuation of treatment in clinical practice (1-3). In this time of growing demands on health-care systems with limited resources, poor adherence further strains the pressure on the limited resources. Poor adherence can reduce the therapeutic effectiveness of these costly treatments or increase medical costs ensuing from the progression of disease and the need of more aggressive treatments (4-6).

National and international recommendations for the use of biologic therapy in RA, SpA, and PsA, cover relevant aspects for clinicians, such as how to reach remission or low disease activity, and are based on evidence and expert opinion (7-9). However, references on adherence to biologics and on strategies to improve it are scarce (10). The paucity of literature on this topic might seem surprising if one takes into account the presence of these drugs in the market over a decade, as well as the availability of large databases documenting their use. But it may be related to its difficult study. The foremost problem for the study of adherence lies in the difficulty and variability of its definition and terminology – compliance, retention, persistence, and alike. In addition, the absence of a reference

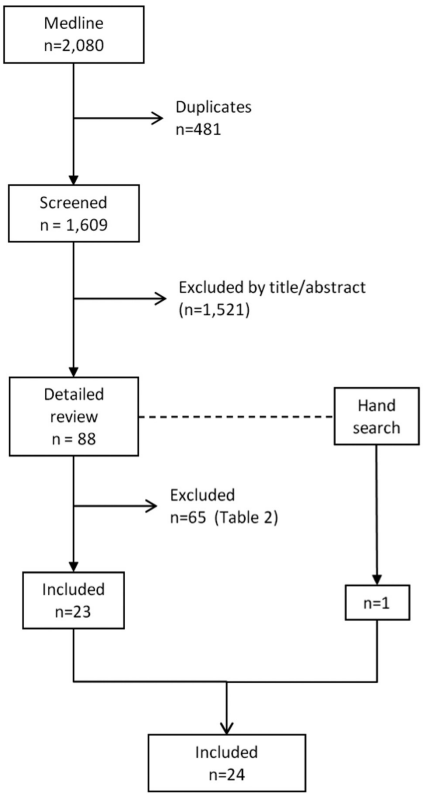

Fig. 1. Articles retrieved, selection and appraisal process.

standard makes the design of tools for measuring it very difficult.

If we want to foster adherence to biologic therapies, we first need to comprehend the problem, to measure it, and to identify modifiable variables that may improve it. With this last aim, we decided, besides other qualitative approaches in parallel, to systematically review the literature available regarding adherence to biologic therapies in RA, SpA and PsA, and its associated factors.

Methods

We performed a systematic literature review to identify predictive factors of adherence to biologic treatments in RA, Spa and PsA patients.

Search strategy

The studies were identified by sensitive search strategies in MEDLINE from 1961 to March 2012 (Table I). We used Mesh terms and text words that were synonyms or close related to adherence, such as "adherence", "patient compliance", "medication adherence", "duration", "survival", "long term survival", "retention", "permanency", "failure", "follow-up", "persistence", "efficiency", "long-term, maintenance". An expert librarian collaborated and checked the search strategies. Language was limited to English and Spanish. A hand search was

Table I. Search strategies for intravenous and subcutaneous biologics.

Search	Intravenous drugs. Query	Items found
#2	Adherence[All Fields]	71008
#3	"patient compliance"[MeSH Terms] OR "compliance"[MeSH Terms] OR compliance [Text Word]	106164
#4	Medication Adherence	9337
#5	Duration	355951
#6	Survival	1119631
#7	Long-term survival	96595
#8	Retention	116040
#9	Permanency	341
#10	Failure	557758
#11	Follow-up	777571
#12	Efficiency	227134
#13	Long-term	464809
#14	Maintenance	187476
#15	("arthritis, psoriatic"[MeSH Terms] OR psoriatic arthritis[Text Word]) OR ("spondylarthritis"[MeSH Terms] OR spondyloarthritis [Text Word]) OR ("arthritis, rheumatoid"[MeSH Terms] OR rheumatoid arthritis[Text Word])	123621
#16	"infliximab"[Supplementary Concept] OR infliximab[Text Word]	7282
#17	"abatacept"[Supplementary Concept] OR abatacept[Text Word]	2125
#18	"rituximab"[Supplementary Concept] OR rituximab[Text Word]	9006
#19	"tocilizumab"[Supplementary Concept] OR tocilizumab[Text Word]	512
#20	(((#19) OR #18) OR #17) OR #16	18336
#21	((((((((((#2) OR #3) OR #4) OR #5) OR #6) OR #7) OR #8) OR #9) OR #10) OR #11) OR #12) OR #13) OR #14	3195816
#22	((#20) AND #21) AND #15	1377
#23	((#20) AND #21) AND #15 Limits: Humans, English, Spanish	1143

Search	Subcutaneous drugs. Query	Items found
#2	Adherence [All Fields]	71008
#3	"patient compliance"[MeSH Terms] OR "compliance"[MeSH Terms] OR compliance[Text Word]	106164
#4	Medication Adherence	9337
#5	Duration	355951
#6	Survival	1119631
#7	Long-term survival	96595
#8	Retention	116040
#9	Permanency	341
#10	Failure	557758
#11	Follow-up	777571
#12	Efficiency	227134
#13	Long-term	464809
#14	Maintenance	187476
#15	("arthritis, psoriatic"[MeSH Terms] OR psoriatic arthritis[Text Word]) OR ("spondylarthritis"[MeSH Terms] OR spondyloarthritis[Text Word]) OR ("arthritis, rheumatoid"[MeSH Terms] OR rheumatoid arthritis[Text Word])	123621
#21	((((((((((#2) OR #3) OR #4) OR #5) OR #6) OR #7) OR #8) OR #9) OR #10) OR #11) OR #12) OR #13) OR #14	3195816
#24	"adalimumab"[Supplementary Concept] OR adalimumab[Text Word] Limits: Humans, English, Spanish Limits: Humans, English, Spanish	0
#25	"adalimumab"[Supplementary Concept] OR adalimumab[Text Word] Limits: Humans, English, Spanish	0
#26	"adalimumab"[Supplementary Concept] OR adalimumab[Text Word]	2516
#27	"TNFR-Fc fusion protein"[Supplementary Concept] OR etanercept[Text Word]	4418
#28	"golimumab"[Supplementary Concept] OR golimumab[Text Word]	170
#29	"certolizumab pegol"[Supplementary Concept] OR certolizumab[Text Word]	322
#30	"interleukin 1 receptor antagonist protein"[MeSH Terms] OR anakinra[Text Word]	3669
#31	((((#26) OR #27) OR #28) OR #29) OR #30	9434
#32	((#31) AND #15) AND #21	1128
#33	((#31) AND #15) AND #21 Limits: Humans, English, Spanish	937

Table II. Excluded studies and reasons for exclusion.

Study	Exclusion reason
Agarwall 2005 (34)	Adherence associated factors were not analysed
Arends 2011 (35)	Adherence associated factors were not analysed
Atzeni 2009 (36)	Adherence associated factors were not analysed
Bartelds 2011 (37)	Adherence associated factors were not analysed
Barthelot 2010 (38)	Adherence associated factors were not analysed
Blum 2011 (3)	Adherence associated factors were not analysed
Coates 2008 (39)	Adherence associated factors were not analysed
Conde-García (40)	Adherence associated factors were not analysed
Delabaye 2010 (41)	Adherence associated factors were not analysed
den Broeder 2006 (42)	Study on anakinra
Dougados 2010 (43)	Adherence associated factors were not analysed
Du Pan 2009 (44)	Adherence associated factors were not analysed
Figueiredo 2008 (45)	Adherence associated factors were not analysed
Fleichsmann 2006 (46)	Adherence associated factors were not analysed
Flendrie 2003 (47)	Adherence associated factors were not analysed
Grijalva 2010 (48)	Adherence associated factors were not analysed
Heldmann 2011 (49)	Adherence associated factors were not analysed
Hyrich 2007 (50)	Adherence associated factors were not analysed
Hyrich 2006 (51)	Adherence associated factors were not analysed
Karlsonn 2008 (52)	Adherence associated factors were not analysed
Klareskog 2011 (53)	Adherence associated factors were not analysed
Konttinen 2007 (54)	Adherence associated factors were not analysed
Levalampi 2010 (55)	Adherence associated factors were not analysed
Lord 2010 (56)	Adherence associated factors were not analysed
Marchesoni 2010 (57)	Adherence associated factors were not analysed
Markeson 2011 (2)	Adherence associated factors were not analysed
Mattey 2009 (58)	Adherence associated factors were not analysed
Mease 2010 (59)	Adherence associated factors were not analysed
Moreland 2006 (60)	Adherence associated factors were not analysed
Oei 2009 (61)	Adherence associated factors were not analysed
Ogale 2011 (62)	Adherence associated factors were not analysed
Saad 2009 (63)	Adherence associated factors were not analysed
Saad 2010 (64)	Adherence associated factors were not analysed
Soderling 2012 (65)	Adherence associated factors were not analysed
Spadaro 2010 (66)	Adherence associated factors were not analysed, n<100
Tanaka 2008 (67)	Adherence associated factors were not analysed
Van der Broek 2010 (68)	Adherence associated factors were not analysed
Vander Cruyssen 2010 (69)	Adherence associated factors were not analysed
Vander Cruyssen 2006 (70)	Adherence associated factors were not analysed
Venetsanopoulou 2007 (71)	Adherence associated factors were not analysed, n<100
Yazici 2009 (72)	Adherence associated factors were not analysed

completed by reviewing the references of the included studies.

Eligibility criteria

The studies retrieved by the above strategies were included if they met the following pre-established criteria:

1. patients aged 18 or older, with a diagnosis of RA, SpA, or PsA;
2. drugs studied were either subcutaneous or intravenous biologics: infliximab (IFX), adalimumab (ADA), etanercept (ETN), tocilizumab (TCZ), rituximab (RTX), abatacept (ABT), golimumab, or certolizumab;
3. only randomised controlled trials (RCT) and high quality cohort studies with a control group and at least 100 patients were selected;
4. studies should include a measurement of adherence and an analysis of predictive or associated factors.

Using these criteria we expected to capture a sufficient number of studies with quality and power enough to test predictors of adherence.

There are different ways to define and to assess adherence (11). The term adherence comprises the "active and voluntary involvement of the patient in a behaviour related to treatment compliance", accepted by mutual agreement with a healthcare professional. A related concept is that of persistence, defined as continued treatment during the period of prescription. Most authors differentiate between measurement of adherence and of persistence, being the medication possession ratio (MPR) and the survival time, or retention rate, the most frequently used parameters to assess both concepts, respectively. In general, the term persistence refers to the continuation of drug use for an overall duration of drug therapy, and adherence refers to the extent of drug use during a period of persistence. Continuation rate, retention rate, and survival time are measures of persistence; MPR – the ratio between the number of days covered by the medication provided and the total number of days of follow-up – and proportion of patients with a MPR value above a certain threshold (in general 80%) are measures of adherence. For the purpose of the present systematic review, both persistence and adherence measures were analysed.

Screening of studies, data collection and analysis

Two reviewers (RLG and LC) screened the titles and abstracts of the retrieved articles for selection criteria independently. Articles without abstracts or with abstract in which fulfilment selection criteria was unclear, were retrieved for detailed review. Thereafter, a third reviewer, EL, screened the full articles for selection criteria and collected the data from the studies included by using *ad hoc* standard forms and performed the hand search. The information collected included description of the study design, sample size, adherence definition and measurement, outcomes, associated factors, and adjustments. To grade the quality, we used an *ad hoc* risk of bias checklist by modification of the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses (12); in addition, we graded evidence using the Oxford Centre of Evidence Levels of Evidence (13). Evidence tables were produced. Meta-analysis was only planned in case enough homogeneity was present among the included studies.

Results

The result of the search strategies is presented in Table I by specific terms, and in total in Figure 1. A total of 1609 articles were retrieved from the search strategy, of which 23 (4-6, 14-33), plus one found by hand search (1), were in-

Table III. Main characteristics of the included studies.

Study	Population/biologic therapies			Adherence	Quality
Borah 2009 (6), USA Retrospective Follow-up 1 yr	n=3,829 RA n=2,537 ETN (78% women, mean age 43 yr), n=1,292 ADA (75% women, mean age 50 yr)			MPR*	Oxford 2c
Brocq 2009 (14), France Retrospective Follow-up 5 yr and 10 m	n=304 AR (mean age) 157 ETN (57 yr) 43 ADA (58 yr) 104 IFX (59 yr)	n=92 EA (mean age) 39 ETA (46 yr) 53 IFX (45 yr)	n=46 PsA (mean age) 32 ETN (49 yr) 5 ADA (58 yr) 9 IFX (48 yr)	Continuation	Oxford 2c
Carmona 2006 (15), Spain National biologics register Follow-up 3 years	n=4,006 RA, n=1,524 SpA ETN, ADA, IFX			Survival	Oxford 2b
Curkendall 2008 (4), USA Retrospective cohort Follow-up 1 yr	n=2,285 RA (75% women, mean age 54 yr) ETN, ADA			MPR*	Oxford 2c
Duclos 2006 (16), France Retrospective 6 yr + Prospective 1 yr	n=440 RA, n=290 SpA ETN, ADA, IFX			Retention	Oxford 2c
Ducourau 2011 (17), France Retrospective Follow-up 3 yr	n=108 (n=17 RA, mean age 48 yr; n=91 SpA mean age 45 yrs) IFX			Survival	Oxford 2c
Fernández-Nebro 2007 (18), Spain Prospective cohort Follow-up 2 yr	n=161 RA n=79 ETN, 76% women n=22 ADA, 82% women n=60 IFX, 88% women			Survival	Oxford 2b
Glintborg 2011 (19), Denmark National biologics register Follow-up 5 yr	n=764 PsA (52% women, mean age 47 yr) n=254 ETN n=320 ADA n=260 IFX			Survival	Oxford 2b
Glintborg 2010 (20), Denmark National biologics register Follow-up 8 yr	n=842 SpA (72% men, mean age 41 yr) n=150 ETN n=247 ADA n=445 IFX			Survival	Oxford 2b
Goekoop-Ruiterman 2007 (21), Holland Survey and information from the BeSt trial Follow-up 2 yr	n=440 RA (68% women, mean age 55 yr) IFX			Protocol adherence	Oxford 1c
Gómez-Reino 2006 (22), Spain National biologics register Follow-up 3 yr	n=4,706 (68% RA, 11% SpA, 10% PsA, 11% other chronic arthritis) ETN, ADA, IFX			Survival	Oxford 2b
Grijalva 2007 (23), USA Prospective cohort Follow-up 9 yr	n=14,932 RA n=78 IFX (75% women, mean age 53 yr) n=374 ETN (78% women, mean age 51 yr) n=120 ADA (81% women, mean age 58 yr) n=98 INF+MTX (77% women, mean age 56 yr) n=262 ETN+MTX (84% women, mean age 53 yr) n=107 ADA+MTX, 79% women, mean age 58 yr)			MPR*	Oxford 2b
Harley 2003 (5), USA Retrospective Follow-up 1 yr and 6 m	n=994 RA n=141 IFX (73% women, mean age 56 yr) n=853 ETN (74% women, mean age 47 yr)			Compliance= MPR>80%	Oxford 2c
Heiberg 2008 (24), Norway National biologics register Follow-up 1 yr	n=1.268 RA 74% women, mean age 52 yr 25% IFX 41% ETA 34% ADA	SPA 26% women, mean age 43 yr 45% IFX 49% ETA 5% ADA	PsA 36% women, mean age 45 yr 28% IFX 59% ETA 16% ADA	Survival	Oxford 2b
Hetland 2006 (25), Denmark National biologics register Follow-up 4 yr	n= 2,326 RA (73% women, mean age 57 yr) 29% ADA 22% ETN 49% IFX			Survival	Oxford 2b

Study	Population/biologic therapies	Adherence	Quality
Kristensen 2008 (26), south of Sweden Local biologics register Follow-up 7 yr	n=261 PsA ETN, ADA, IFX	Survival	Oxford 2c
Kristensen 2010 (27), south of Sweden Local biologics register Follow-up 2 yr	n=243 SPA (73% men, mean age 43 yr) ETN, ADA, IFX	Survival	Oxford 2c
Kristensen 2006 (28), south of Sweden Local biologics register Follow-up 5 yr and 9 m	n=1,161 RA ETN, ADA, IFX	Survival	Oxford 2c
Leffers 2011 (29), Denmark National biologics register Follow-up 1 yr	n=328 RA n=150 ABT (77% women, mean age 45 yr) n=178 TCZ (74% women, mean age 56 yr)	Survival	Oxford 2b
Li 2010 (1), USA Retrospective Follow-up 1 yr	n=2,638 RA n=1,359 ETN (88% women, mean age 54 yr) n=267 anakinra (91% women, mean age 55 yr) n=1,012 IFX (77% women, mean age 63 yr)	PDC†	Oxford 2c
Pavelka 2009 (30), Check Republic National Register Follow-up 1 yr	n=310 SPA n=127 ETN (72% women, mean age 36 yr) n=30 ADA (67% women, mean age 34 yr) n=153 INF (82% women, mean age 37 yr)	Survival	Oxford 2b
Punzi 2011 (31), Italy Retrospective Follow-up 36 m	n=703 RA n=259 ETN (80% women, mean age 54 yr) n=196 ADA (83% women, mean age 53 yr) n=248 IFX (80% women, mean age 52 yr)	Survival	Oxford 2c
Yamanaka 2010 (32), Japan Retrospective cohort Follow-up 1 yr	n=229 RA (84% women, mean age 58 yr) TCZ	Survival	Oxford 2c
Zink 2005 (33), Germany National Register Follow-up 1 yr	n=854 RA n=511 ETN (78% women, mean age 53 yr) n=343 IFX (71% women, mean age 53 yr)	Survival	Oxford 2b

USA: United States of America; yr: year; m: month; RA: rheumatoid arthritis; SpA: spondyloarthritis; PsA: psoriatic arthritis; INF: inflixmab; ADA: adlimumab; ETN: etanercept; ABT: abatacept; TCZ: tocilizumab; MTX: methotrexate.
*MPR: medical possesion rate.
†PDC: proportion of days covered= measured as the number of days covered with biologic divided by the fixed time interval of 365 days from date of index biologic therapy initiation.

cluded. Excluded studies and reasons of exclusion are shown in Table II.

Table III shows the main characteristics of the selected studies. Most studies were observational studies of good quality (graded evidence Oxford 2b-c); one was a RCT (21). The majority included RA patients (n=19), 9 analysed data from patients with SpA and 5 patients with chronic arthritis in general. The duration of follow-up varied from 1 to 9 years. With regard to specific biologic drugs, IFX, ETN and ADA were the most frequently analysed, although data on abatacept and tocilizumab are also provided. There is a great variability in relation to the adherence definition, measurement methods and associated factors analysed. Survival time of the biologic drug was the most common measure of persistence (n=16), while the MPR, or proportion of days covered by medication, was the usual method to assess adherence (n=5). In the included studies different predictors were analysed.

Concept and definition of adherence

There is a great variability in the definition and measurement methods of adherence, a widely recognised phenomenon in the literature. Most studies focused on persistence, or continued treatment during the period of prescription, as measured by survival time and retention or continuation rates (14-20, 22, 24-33). Fewer publications opted for adherence determined by the MPR, or proportion of days covered by medication during the follow-up, with a cut-off ≤80% (1, 5, 6, 21). In two studies both adherence and persistence of biological therapy were measured, by MPR and survival time, respectively (4, 23).

Biologic drugs

Overall, the results show that adherence to ETN (expressed as MPR or survival time) is usually superior to that of ADA or IFX (6, 14, 18, 22, 25, 26, 28, 31) in both, naïve and existing users (6, 18), and generally higher for the first cycle than consecutives (22). However, some authors have not found any differences between TNF blockers (16, 19, 20, 27, 30), and even in one case adherence was greater for IFX than for ETN (1). Likewise, it is possible that higher doses of IFX are associated with better adherence (18). A further consideration to take into account is that some of these results are in raw form and not adjusted for potential confounders (14, 30, 31).

Table IV. Main results of the included studies.

Study Disease	Adherence	Biologics	Unadjusted analysis	Adjusted analysis	Adjusting covariates
Borah (6) 2009 RA	MPR*	ADA ETN	Naïve patients: no differences (p=0.731) Patients already on medication: ETN > ADA (p=0.051)	Non-adherent (Naïve users): – ADA *vs*. ETN: OR=1.24 (95% CI 0.08 0.97-1.58) – Age: OR=0.98 (95% CI 0.97-0.99) – MTX use: OR=0.54 (95% CI 0.42-0.68) – other DMARDs use: OR=0.67 (95% CI 0.51-0.87) Non-adherent (Existing users): – ADA *vs*. ETN: OR=1.25 (95% CI 0.01 1.05-1.49) – Age: OR=0.97 (95% CI 0.96-0.98) – MTX use: OR=0.79 (95% CI 0.65-0.97) – other DMARDs use: OR=0.82 (95% CI 0.7-0.97) – female genital disease*: OR=0.83 (95% CI 0.68-1.01) – non-traumatic joint disease*: OR=0.22 (95% CI 0.07-0.66) – symptoms, signs, ill-defined conditions: OR=1.24 (95% CI 1.01-1.52) – diabetes: OR=1.69 (95% CI 1.24-2.30)	Age, gender, MTX use, DMARDs use, Northeast, south, west Visits: ambulatory, ER, IP Diseases: – female genital organs – respiratory infections – non-traumatic joint and other connective tissue – symptoms, signs and ill-defined conditions – residual codes, unclassified, E code – lupus, hypertension, immunisation – screening for infectious disease – eye disorders – spondylosis; intervertebral disc disease; other back problems – liver and heart disease; lower respiratory disease – lipid metabolism, skin disorders – diabetes, cancer, asthma; – headache and migraine
Brocq (14) 2009 RA, SpA, PsA	Continuation rate	IFX ETN ADA	Continuation rate RA: ETA *vs*. ADA *vs*. INF – 12 months: 87% *vs*. 83% *vs*. 68% – 24 months: 68% *vs*. 66% *vs*. 46% – INF *vs*. ETA p=0.0001; INF *vs*. ADA p=0.01 Continuation rate AS: INF *vs*. ETA – 12 months: 89% *vs*. 76% (p=0.03) PsA: No differences between therapies (p>0.050)	–	–
Carmona (15) 2006 RA, SpA	Survival	IFX ETN ADA	Survival – SpA > RA (1st, 2nd, 3rd yr)(p<0.001) – IFX 1st biologic: SpA > RA (p=0.007) – ETN 1st biologic: SpA > RA (p=0.044) – No survival differences between diseases with IFX or ETN as 2nd biologic	HR for discontinuation (95% CI): – SpA *vs*. RA: HR=0.66 (0.57-0.76) – Older than 60: HR=1.21 (1.08-1.36) – Being female: HR=1.27 (1.13-1.43) – Using infliximab: HR=0.66 (0.57-0.76)	– Type of disease – Age – Gender – Use of infliximab
Curkendall (4) 2008 RA	Adherence (MPR) Persistence (survival)	ADA ETN	–	MPR (linear regression model) – Greater patient's share of costs, coef= -0.0035; (p<0.001) – female gender, coef=-0.044 (p=0.002) – HMO insurance, coef=-0.091 (p<0.001) – Northeastern USA region, coef=0.036 (p=0.004) – Prescriptions for DMARDs 6 m prior, coef=0.064 (p=0.003) Survival (Proportional hazard ratio model) – OOP costs, HR=1.58 (p<0.001) – Charlson score, HR=1.07 (p=0.003) – Age, HR=0.996 (p=0.034)	Variables with p-value ≥0.10 in the bivariate analysis: – Demographic characteristics – Type of insurance – patient status (insured *vs*. dependent) – Charlson score, preexisting comorbidities – DMARDs in the previous 6 m – use of NSAID or narcotic analgesics – hospitalisations, number of visits to a physician
Duclos (16) 2006 RA, SpA	Retention rate	IFX ETN ADA	–	Retention – No difference between 3 TNF blockers (p=0.48) – 1st anti-TNF course (all patients); HR=2.17 (95% CI 1.82-2.58) – No concomitant DMARD (all patients); HR=0.70 (95% CI 0.51-0.97) – SpA: HR=1.60 (95% CI 1.2-2.13) – RA no retention changes with anti-TNF + MTX (p=0.590) – SpA no differences with the use of concomitant DMARD or MTX (p=0.13, p=0.90)	Variables with p-value >0.20 in the bivariate analysis: not specified
Ducourau (17) 2011 RA, SpA	Survival	IFX	RA – IFX concentration > than median not associated (p=0.060) – IFX concentrations > than 1st quartile not associated (p=0.200) SPA – IFX concentration > than median (p=0.060) – IFX survival > if IFX concentrations > than 1st quartile (p=0.050)	–	–

Study Disease	Adherence	Biologics	Unadjusted analysis	Adjusted analysis	Adjusting covariates
Fdez-Nebro (18) 2007 RA	Survival	IFX ETN	Survival (anti-TNF naïve RA patients) – ETN > IFX at 2 yr (p=0.032) – FX scale-up regime of 5mg/kg/8w (p=0.043)	Lower probability of premature failure – Adherence: HR=0.39 (0.18-0.86) – Dose escalation of INF: HR=0.35 (0.18-0.71) – ETN *vs*. INF: HR=0.34 (0.18-0.61)	Variables with p-value <0.10 in bivariate analysis: – Sex, age, duration of disease – Charlson comorbidity index – RF, DAS28, HAQ, ESR, RCP – Adherence, year of first anti-TNF
Glintborg(19) 2011 PsA	Survival	IFX ETN ADA	Survival – Similar among anti-TNFs, no association with concomitant MTX (p>0.050) – Male gender (p<0.001) – CRP level > 10 mg/L (p=0.006) – Baseline patient health VAS ↓(p=0.005)	Factors associated with shorter drug survival – Female sex: HR=1.42 (p=0.005) – VAS global score at baseline: HR=1.10 (p=0.001) – CRP at baseline (≤10 mg/l): HR=1.40 (p=0.008) – No concomitant MTX use: HR=1.37 (p=0.013)	– Sex, age, disease duration – Swollen and tender joints counts – VAS,HAQ, DAS28 scores – Baseline CRP level – Baseline MTX use
Glintborg (20) 2010 SpA	Survival	IFX ETN ADA	Survival – Similar among anti-TNFs (p=0.20) – No association with VAS pain, VAS global, BASFI (p>0.050) – Male gender (p<0.001) – Baseline BASDAI ↓ (p=0.007) – VAS fatigue ↓ (p<0.001) – Baseline CRP level >14 mg/L (p<0.001) – Baseline BASFI ↓ (p=0.003)	Factors associated with shorter drug survival – Female sex: HR=1.46 (p=0.02) – VAS fatigue: HR=1.14 (p<0.01) – CRP at baseline (≤14 mg/l): HR=1.53 (p=0.05)	– Sex, age – BASDAI, BASFI – VAS (pain) – VAS (global) – CRP level – MTX use – Biological treatment
Goekoop-Ruiterman (21) 2007 RA	Protocol adherence	IFX	No protocol adherence differences between patients with or without preference for a particular treatment group	–	–
Gómez-Reino (22) 2006 RA, SpA, PsA	Survival	IFX ETN ADA	Survival – 1st anti-TNF during the 1st yr – IFX (81%) < ADA (87%)< ETN (88%); p<0.05 – 2nd anti-TNF – IFX (34%)< ADA (67%); ETN (76%) <; p<0.05	Discontinuation of first treatment – INF: HR=1.50 (95% CI: 1.27-1.77) – Diagnosis of RA: HR=1.36 (95% CI: 1.18-1.56) – Discontinuation of second treatment – INF: HR=3.83 (95% CI: 2.58-5.68) – Suspension of first treatment by adverse event: HR=0.54 (95% CI: 0.34-0.84)	Discontinuation of first treatment – Age, sex group – TNF antagonist – Diagnosis (RA, AE, PsA, JIA, others) – Discontinuation of second treatment – Age, sex group – TNF antagonist – Diagnosis (RA, AE, PsA, JIA, others) – Reason for discontinuation of the first treatment
Grijalva 2007 (23) RA	MPR* (Adherence) Persistence (Survival)	IFX ETN ADA	MPR (MTX as reference) – IFX: coef=0.10 (95% CI 0.05-0.15) – ETN: coef=0.03 (95% CI 0.01-0.05) – ADA: coef=0.05 (95% CI 0.02-0.08) – IFX+MTX: coef=0.12 (95% CI 0.18;0.07) – ETN+MTX: coef=0.12 (95% CI 0.15;0.09) – ADA+MTX; coef=0.06 (95% CI 0.1;0.02) Persistence (MTX as reference) – IFX: HR=1.52 (95% CI 1.21-1.89) – ETN: HR=0.87 (95% CI 0.78-0.98) – ADA: HR=0.96 (95% CI 0.76-1.2) – IFX+MTX: HR=1.02 (95% CI 0.82-1.28) – ETN+MTX: HR=1.06 (95% CI 0.92-1.24) – ADA+MTX; HR=0.68 (95% CI 0.51-0.9)	MPR (MTX as reference) – IFX: coef=0.11 (95% CI 0.06-0.16) – ETN: coef=0.04 (95% CI 0.02-0.06) – ADA: coef=0.04 (95% CI 0.01-0.08) – IFX+MTX: coef=0.12 (95% CI 0.17;0.07) – ETN+MTX: coef=0.11 (95% CI 0.14;0.08) – ADA+MTX; coef=0.07 (95% CI 0.11;0.03) Persistence (MTX as reference) – IFX: HR=1.37 (95% CI 1.09-1.73) – ETN: HR=0.82 (95% CI 0.73-0.92) – ADA: HR=0.85 (95% CI 0.67-1.08) – IFX+MTX: HR=0.91 (95% CI 0.73-1.15) – ETN+MTX: HR=1.01 (95% CI 0.87-1.17) – ADA+MTX; HR=0.63 (95% CI 0.48-0.84)	Age, sex, race – Calendar year, residence location – Disability – Residency in nursing home – Risk score – To account for measured confounders and to reduce the number of covariates in the regression models, a summary risk score was created
Harley (5) 2003 RA	Compliance= MPR>80%	IFX ETN	–	Compliance – IFX > ETN; OR=0.46 (95% CI 0.29-0.74)	Age, sex, baseline cost, type of insurance, region, comorbidities, RA concomitant/ prior medications, type of physician
Heiberg (24) 2008 RA, SpA, PsA	Survival	IFX ETN ADA	1 year retention rate – 65%, 77% and 77% for RA, PsA and AS, respectively – RA *vs*. PsA: p=0.003 – RA *vs*. AS: p=0.001 – Monotherapy vs Combination therapy – anti-TNF+MTX > anti-TNF in RA (p<0.001) and PsA (p=0.020) –No differences in AS (p=0.290)	Adjusted treatment discontinuation – PsA *vs*. RA: HR=0.76 (95% CI: 0.47-0.92) – AS *vs*. RA: HR=0.66 (95% CI: 0.47-0.92) – Female: HR=1.51 (95% CI: 1.19-1.93) – VAS investigator's global: HR=1.06 (1.001-1.13) – Concomitant MTX: HR=0.53 (95% CI:0.43-0.65)	– Age, sex – Investigator's global assessment – Concomitant MTX
Hetland (25) 2010 RA	Survival	IFX ETN ADA	Best survival ETN, worst IFX (p<0.0001): – ETN=56% (95% CI 51-62%) – ADA=52% (95% CI 46-57) – IFX=41% (95% CI 37-44)	– INF *vs*. ADA: HR=1.35 (1.15-1.58) – INF *vs*. ETA: HR=1.98 (1.63-2.40) – ADA *vs*. ETA; HR=1.47 (1.20-1.80)	– Age, disease duration – Baseline disease activity, seropositivity – Concomitant MTX and prednisolone – Number of previous DMARD – HAQ score
Kristensen (26) 2008 PsA	Survival	IFX ETN ADA	–	Better overall drug survival: – Concomitant MTX: HR=0.64 (p=0.030) – ETA *vs*. INF: HR=0.49 (p=0.01) – High CRP: HR=0.77 (0.03) – no associated with dosage level or cessation of MTX – ETN > IFX, (p=0.010) – No differences between IFX and ADA (p=0.120), or ADA and ETN (p=0.960)	– Age, sex, patient VAS global – PsA duration, pattern of joint distribution – Concomitant NSAIDs, previous nº of DMARD, – Concomitant NSAID usage – Pattern of joint distribution – Previous number of DMARD – VAS global – Disease duration

Study Disease	Adherence	Biologics	Unadjusted analysis	Adjusted analysis	Adjusting covariates
Kristensen (27) 2010 SpA	Survival	IFX ETN ADA	Survival (1 and 2 yr) – Peripheral arthritis > axial disease (p=0.050) Survival (12 and 24 m) – VAS global improvement (p<0.010)	Survival: 2-year drug continuation rate 74% Predictors of better survival: – Male sex: HR=0.36 (95% CI 0.19-0.68) – Peripheral arthritis: HR=0.49 (95%CI 0.27-0.88) Trends to better survival, but not significant: – Concomitant DMARD; HR=0.61 (95% CI 0.34-1.10) – Higher baseline CRP; HR=0.99 (95% CI 0.97-1.00) – No differences between anti-TNF – ENT *vs*. IFX; HR=0.50 (95% CI 0.25-1.04) – INF *vs*.ADA; HR=1.40 (95% CI 0.58-3.42)	– Covariates entered based on correlation, previous reports, clinical relevance: – Disease duration, age, sex, CRP level – Clinical phenotype: axial SpA *vs*. peripheral arthritis – Type of anti-TNF, concomitant DMARD – BASDAI, BASFI, HAQ, VAS global, global evaluation scores
Kristensen (28) 2006 RA	Survival	IFX ETN ADA	Survival – Anti-TNF + MTX > anti-TNF (p<0.001) – Anti-TNF + MTX > anti-TNF + other DMARD (p<0.010) – IFX < ETN (in patients with concomitant MTX or other DMARDs or in monotherapy), p<0.001 – IFX/ETN + MTX > IFX/ETN (p<0.001) – IFX+ MTX > IFX + other DMARDs (p=0.002) – No difference for ETN – ETN + DMARD > ETN (p=0.015)	Survival – High CRP level at treatment initiation (irrespectively of anti-TNF), HR=0.90 (95% CI 0.81-0.98) – ETN + MTX > IFX + MTX, HR=3.27 (95% CI 1.76-6.08) – ETN > IFX, HR= 4.26 (95% CI 2.60-7.00) No association (p>0,050) with: gender, yr of treatment initiation, DAS28, disease duration prior to treatment initiation	– Age, gender, CRP level, DAS28 – HAQ score, disease duration – Previous and concomitant DMARDs – Year of initiation
Leffers (29) 2011 RA	Survival	ABT TCZ	–	Survival – ABT: no predictors (all p>0.050) – TCZ: lower with higher baseline DAS28 – HR=0.95/DAS28 unit ↑ (0.91-1.00/DAS28 unit ↑), p=0.048	Demographic and clinical variables related to RA activity
Li (1) 2010 2010 RA	PDC† ≥80%	Anakinra IFX ETN	PDC – Anakinra < ETN and IFX, in general and in patients with concomitant DMARDs (p<0.050)	Adherence /non adherence (PDC† ≥80%) – Other races > whites; OR=1.29 (95% CI 1.02-1.63) – Florida < other states, OR=0.67 (95% CI 0.52-0.86) – Oral DMARD in the 12-m pre-index period, OR=1.27 (95% CI 1.00-1.62) – IFX > ETN, OR=1.47 (95% CI 1.18-1.83) – Anakinra < ETN, OR=0.27 (95% CI 0.17-0.42)	– Age, sex, race, index date, state
Pavelka (30) 2009 SpA	Survival	IFX ETN ADA	Survival anti-TNF SPA > RA p<0.001 – 1st y: 84% (95% CI 80-88%) vs 78% (95% CI 75-81%) – 2nd y 76% (95% CI 71-81%) vs 59% (95% CI 55-62%) – 3rd y 72% (95% CI 67-78%) vs 49% (95% CI 46-53%) – No differences among anti-TNFs (p=0.057) – Risk factor for treatment discontinuation – Male gender > female gender, RR=2.22 (p=0.001) – Increased CRP value, RR=1.33 (p=0.025)	–	–
Punzi (31) 2011 RA	Survival	IFX ETN ADA	– Survival IFX < ETN and ADA (p<0.001) – No differences between ADA and ETN (p>0.050)	–	–
Yamanaka (32) 2011 RA	Survival	TCZ	Retention rate 79% at 24 months – No differences with concomitant/not MTX (p=0.197) – No differences with previous/not anti-TNF (p=0.892)	–	–
Zink (33) 2005 RA	Survival ETN	IFX	Continuation rates – Similar for ETN (69%) and INF (65%) at 1 yr – No differences ETN+MTX or other DMARD with ETN (p>0.050) – No differences IFX+MTX or other DMARD with IFX (p>0.050)	Predictors of premature treatment termination: – No. of previous DMARDs, HR=1.09 (95% CI 1.01-1.18) – RF, HR=1.53 (95% CI 1.09-2.16) – Age, HR=1.01 (95% CI 1.00-1.02) – INF *vs*. INF+MTX, HR=1.9 (95% CI 1.1-3.1) – ETN *vs*. ETA+DMARD=1.3 (95% CI 0.9-1.8)	– Age and sex – Number of previous DMARD – Rheumatoid factor – DS28 – Tender and swollen joint counts – HAQ – Disease duration

USA: United States of America; yr: year; m: month; RA: rheumatoid arthritis; SpA: spondyloarthritis; PsA: psoriatic arthritis; INF: inflixmab; ADA: adlimumab; ETN: etanercept; ABT: abatacept; TCZ: tocilizumab; MTX: methotrexate; DMARD: disease modifying drugs; Dis: diseases; ER: emergency room; IP: inpatient; OOP: out of pocket; HMO: Health Maintenance Organisation; RR: risk ratio; CI: confidence interval; yr: year; mg: milligram; kg: kilogram; w: week; L: liter; CRP: C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; VAS: visual analogue scale; HAQ: Health Assessment Questionnaire; DAS-28=28-joint Disease Activity Score; Coef=coefficient; CRP= C reactive protein

*MPR: medical possesion rate. †PDC: proportion of days covered: measured as the number of days covered with biologic divided by the fixed time interval of 365 days from date of index biologic therapy initiation.

Information on all other biologics is very limited.

Adherence by disease

Although in most of the selected studies no comparisons on adherence between different diseases were conducted, the results suggest that adherence to biologic therapy, at least to the three mainly TNF blockers (ADA, ETN, and IFX), is superior in SpA than in RA (14-16, 22, 24, 30).

Predictive factors

Age. The effect of age on adherence to anti-TNF is unclear. According to the results of some studies, age decreases the risk of non-adherence in both naïve users as existing users (6). However, other authors have observed that the probability of treatment discontinuation increases significantly in persons older than 60 (15), while in other cases the survival of biological discreetly increases with age (4).

Gender. In general, women are less adherent than men, both in terms of persistence (15, 19, 20, 24) and MPR (4), although other authors have found no association between drug survival and sex (28).

Comorbidity. Borah *et al*. studied the effect of different diseases on non-adherence in patients already on medication (6). The results showed greater adherence in patients with female urogenital tract conditions and non-traumatic joint diseases, while other ill-defined conditions and diabetes increased the likelihood of non-adherence, expressed by MPR (6). On the other hand, Curkendall *et al*. observed a decreased survival of ETN and ADA with higher Charlson comorbidity score (4).

Disease activity. A poor clinical condition at baseline, measured by different parameters, such as VAS global, or fatigue scores, is associated with lower drug survival (19, 20, 24). However, a high baseline C-reactive protein improves overall anti-TNF survival in some studies (26, 28), although not in all in which this was analysed (27). Rheumatoid factor positivity also increases the likelihood of premature treatment discontinuation (33).

Concomitant DMARD. The relation between previous or concomitant use of DMARDs and the adherence to TNF blockers is not consistent across the included studies. MTX and other DMARDs can increase the adherence (1, 4, 6, 16, 19, 24, 26, 27), but the number of previous DMARDs is associated with premature treatment discontinuation (33).

There have been few studies comparing the effects of anti-TNF, monotherapy or combination therapy, versus MTX monotherapy. Grijalva *et al*. evaluated the adherence and persistence during episodes of new biologic drugs. Compared to MTX courses, new mono-INF courses were more likely to be discontinued, and new episodes of mono-ETN and of ADA+MTX were less likely to be discontinued (23).

Other. Other factors such as geographic localisation, weekly patient (out-of-the-pocket) OOP costs, co-payment or some charge to the patients, and type of medical insurance can also influence biologic drug adherence (4).

Discussion

The beneficial effects of therapeutic interventions necessarily entail the compliance or adherence of the patient with the prescribed recommendations. In contrast to this apparent obviousness, lack of compliance is a common problem causing significant impact on the efficacy of treatment and health costs of patients with chronic diseases. In the present study we have analysed the adherence to biologic therapy in RA, SpA and PsA patients, as well as their associated factors. For the purpose of the present systematic review, it was decided to include randomised and cohort controlled studies as the most appropriate way to answer the research question.

Overall, the evidence on adherence varies widely, likely due to the difficulty and different aspects of its definition and the lack of a single method for its determination. The absence of a method to assess all aspects of compliance makes some authors recommend the combined use of different tools. However, most of the articles selected used persistence, few MPR, and only two studies studied simultaneously the adherence and persistence of biological therapy (4, 23). Interestingly, the results of adherence and persistence seldom are in the same direction, which could be explained by the complexity of the concepts and of the adjustment.

The evidence on differences in adherence to various anti-TNF is not conclusive. Although many authors find superiority of ETN over IFX and ADA (6, 14, 18, 22, 25, 26, 28, 31), these results are not evident in other cases, (16, 19, 20, 27, 30), probably related to methodological differences and potential confounders. Moreover, persistence of the three main TNF blockers is consistently higher in SpA than in RA, both in retrospective studies (14, 16) and in national or local prospective biologic registers (15, 22, 24, 30). In relation to the effect of previous or concomitant use of DMARDs, the results are not consistent across different studies (1, 4, 6, 16, 19, 24, 26, 27).

This review has identified associated factors to TNF blockers that may increase the adherence, such as age (6), or decrease it, such as female gender (15, 19, 20, 24), comorbidity (4), a poor clinical condition at baseline (19, 20, 24), presence of rheumatoid factor (33) or the number of previous DMARDs (33). Unfortunately, there is little room for modification there. Other associated factors, such as weekly patient out-of-the-pocket expenses, co-payment, or some charge to the patients, and type of medical insurance can also influence to the biologic drug adherence (4), but here rheumatologists can do very little.

It is very important to emphasise the limitations of this review. We used Medline only to recover the articles, which may have resulted in less articles and from different locations than by searching in more databases; however, we doubt that the quality of the finally included articles would have been greater, and the results more conclusive.

Conclusion

Because of the limitations of the available data, these results indicate adherence may differ among the main anti-TNF and also among different rheumatic diseases. However, the reasons underlying these differences have not

been finely explored. Unfortunately, no modifiable factors were explored by the included studies neither, making this strategy of a systematic review to improve adherence by looking only at studies that studied adherence on biologics frustrating. Future studies should aim to explore adherence to biologics, preferably by more than a definition, and its association to modifiable factors.

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