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REVIEW

A Targeted Literature Review Examining Biologic Therapy Compliance and Persistence in Chronic Inflammatory Diseases to Identify the Associated Unmet Needs, Driving Factors, and Consequences

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Abstract: Chronic inflammatory diseases (CIDs) represent a substantial clinical and economic burden to patients, providers, payers and society overall. Biologics, such as tumor necrosis factor inhibitors (TNFi), have emerged as effective treatment options for patients with CIDs. However, the therapeutic potential of biologics is not always achieved in clinical

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practice, with results from studies examining the use of biologics in real-world settings suggesting lower levels of treatment effectiveness compared with clinical trial results. Using a targeted approach, this literature review demonstrates that compliance and persistence with biologic therapy is suboptimal and that this has implications for both clinical outcomes and treatment costs. The review identified a variety of predictors of treatment compliance and persistence, including increased age, female gender, presence of comorbidities, increased disease activity, longer disease duration, smoking, increased body mass index, higher biologic treatment dose, higher treatment cost and lower health-related quality-of-life scores. Patients often cited factors associated with medication delivery as a reason for non-compliance and non-persistence, and device-related improvements to treatment delivery were associated with higher rates of compliance and persistence. The articles identified in this review provide insights that have the potential to help guide the development of new solutions to improve disease management and optimize treatment regimens. This has the potential to benefit patients' health by improving clinical outcomes and to reduce the burden to society by limiting the economic impact of patients' disease.
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INTRODUCTION

Chronic inflammatory diseases (CIDs) are a group of related autoimmune diseases that include rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), inflammatory bowel disease (IBD), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), psoriasis (PsO) and Crohn's disease (CD). Together CIDs affect between 5 and 7% of the Western population [1] and represent a significant economic and societal burden [2]. As a consequence of the inflammation and loss of function of the affected tissue, these conditions are associated with chronic disability, significant pain and reduced functional impairment (in arthritic conditions). Patients require long-term therapy and often have significantly reduced productivity and quality of life, increased morbidity and premature mortality [2].

Biologics have emerged as effective therapeutic options for patients with CIDs who fail to respond to first-line treatments such as methotrexate [3]. For example, clinical trials examining the efficacy and safety of tumor necrosis factor inhibitors (TNFi) have demonstrated that disease remission is a realistic target for some of these patients [3, 4]. It is difficult to compare randomized-controlled trials (RCTs) with real-world studies since measures of effectiveness may not be the same, co-therapy changes are frequent, therapy patterns are not dictated by protocols, and patient heterogeneity in real-world studies results in broader populations under medication. However, the biologic therapeutic potential observed in clinical trials is rarely achieved in clinical practice, with results from studies examining the use of biologics in real-world settings suggesting lower levels of treatment effectiveness [5, 6]. In real-world clinical settings, recommended treatment regimens are not always adhered to. This may be due to a variety of factors including physicians tailoring therapy to patients' needs, for

example, guided treatment withdrawal [7, 8]; however, a number of studies have also reported suboptimal patient compliance and persistence with biologic therapy, which may reduce the clinical effectiveness of the prescribed treatment [9–11].

Generally, comparing studies is challenging as a plethora of definitions are used to describe compliance and persistence, and study designs often vary. There is evidence that factors associated with patients' experience during treatment, and not solely those linked to the efficacy and safety of a drug, may play a role. For example, biologics are often administered by self-injection, which can be associated with significant patient anxiety [12, 13]. Although there are clear challenges to understanding the causes leading to non-compliance and non-persistence, understanding the driving factors represents a potential opportunity to reduce the burden associated with CIDs by maximizing treatment effectiveness, ensuring the full efficacy potential of biologics is achieved.

Here we report the findings from a review of the available literature on compliance and persistence with biologic therapies across multiple conditions including axSpA, CD, IBD, JIA, PsA, PsO and RA. The aims of this review were to: (1) provide an overview of compliance and persistence with biologic therapeutics in the context of CIDs, aligning the studies to predefined definitions of persistence and compliance, (2) examine the impact of any treatment-related factors identified as contributing to non-compliance and non-persistence, focusing on the impact of using different self-injection devices and patient-support services and (3) review the clinical and economic consequences of suboptimal treatment compliance and persistence.

METHODS

Search Strategy and Study Selection

Two targeted literature searches were performed. The first was designed to provide a broad overview of the comparative landscape of anti-TNF biologic therapies used to treat CIDs. Electronic searches were performed in PubMed/

MEDLINE for indexed literature published between January 2000 and October 2015. The search strategy identified literature reporting economic, clinical and health-related quality of life (HRQoL) outcomes associated with the use of different biologic therapies. The search terms used included the specific disease indications (RA, CD, PsA, AS, axSpA, PsO, JIA, pediatric CD and uveitis), economic outcomes (e.g., 'resources', 'costs'), and clinical and HRQoL outcomes (e.g., 'ASAS20', 'BASMI', 'IBDQ', 'work impairment'). Electronic searches were complemented by a review of conference proceedings [European League Against Rheumatism (EULAR), American College of Rheumatology (ACR), International Society for Pharmacoeconomics and Outcomes Research (ISPOR), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP)], ClinicalTrials.gov and therapy manufacturers' websites from the preceding 2 years.

The second targeted literature search was designed to identify any additional studies published after 2015 that reported data on the impact of devices on compliance and persistence and on the clinical and economic outcomes related to non-compliance and non-persistence. The search was conducted in OVID (including MEDLINE, EMBASE, CRD, Cochrane, Econlit and the ACP Journal Club) for indexed literature published between January 2015 and May 2017. In addition, the bibliographies of key review articles were manually reviewed to supplement the electronic searches.

For both searches, English language studies were included if they could be described as real-world data studies, such as observational studies using databases and registries, pragmatic clinical trials, phase IV trials/post-marketing open-label/'off-label' studies, patient and population surveys, chart reviews or economic models based on real-world data. Once the selection criteria had been applied to all identified studies, included publications were grouped according to their reported outcomes as described below.

Definitions Used to Align Measures of Persistence and Compliance

The definitions used by researchers to define compliance and persistence, the use of different data sources (e.g., prescription data, patient self-reported measures and doctors' observations) and methods used to calculate rates, and the geographic location of the health system can all influence the reported values of compliance and persistence.

For this review, all included studies were examined to identify the methods used to calculate rates of compliance and persistence. These methods were compared with the definitions recommended by ISPOR, described below, to categorize the studies as compliance- or persistence-focused as appropriate: [14]

- *Compliance*: The extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen.
- *Persistence*: The duration of time from initiation to discontinuation of therapy.

Both compliance and persistence are calculated using a number of different methods. Compliance can be calculated using the Medication Possession Ratio (MPR, the proportion of days' supply for all fills of a drug in the total medication period) and/or the Proportion of Days Covered (PDC; defined as the proportion of days a patient is 'covered' by their drug supply in the medication period). In the event of overlapping refills, PDC will not change while the MPR value will be higher. MPR and PDC data do not necessarily take into account when patients are following their treatment regimen or how optimal the regimen is, but rather whether they are in possession of treatment. Consequently, they may underestimate the rates of non-compliance [15].

Persistence can be described using either the continuation rate (also known as the retention rate and defined as the proportion of patients adhering to a given treatment in a given time) [16] or drug survival (defined as the number of days individual patients maintained treatment) [14].

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Search Results

The initial literature search identified 7823 studies of potential interest via PubMed, 6857 documents from conference proceedings and 673 clinical trials. Following the final application of the eligibility criteria (Table 1), 125 peer-reviewed studies (Supplementary Figure S1), 109 conference abstracts/posters, and 20 ongoing or completed clinical trials, identified from ClinicalTrials.gov, were included for review. The literature review update identified an additional 826 publications of potential interest via PubMed, Embase, Cochrane, CRD, Econlit, ACP Journal Club and conference proceedings. From this search, a further 17 relevant studies were identified and included for review (Supplementary Figure S2).

Overview of Compliance and Persistence with Biologic Therapy

In total, 19 publications reporting compliance data, and 110 publications reporting persistence data were identified during the first literature search.

The majority of studies reported on the treatment of RA patients with conventional biologics such as etanercept, adalimumab and infliximab. The methodology, study designs, patient populations and time points used to measure compliance and persistence were highly inconsistent, leading to a wide range of reported estimates. Across all the literature reviewed, rates of persistence and compliance varied considerably (Supplementary Table S1). Of the studies reviewed, approximately one-third (n = 32) provided information on previous biologic experience.

Table 1 Inclusion and exclusion criteria for study selection during review

Inclusion criteria

Studies in the English language

Real-world data studies, such as observational studies using databases and registries, pragmatic clinical trials, phase IV trials/post-marketing open-label/'off-label' studies, patient and population surveys, chart review, economic models based on real-world data

Publications based on original research

Interventions including TNFi, other biologics with alternative MOA or JAK inhibitor treatment

Patients studied with any of the following diseases: RA, PsO, PsA, JIA, AS, axSpA, nr-axSpA, uveitis, CD and pediatric CD

Treatment persistence, adherence and/or compliance was included as an outcome

Exclusion criteria

Interventional studies

Review and meta-analyses on RCTs that do not include RWE based on the abstract

In vitro/pre-clinical studies

Non-human studies

Economic models based on data other than cohorts or other RWE

Guidelines, letters, editorials

Review articles; however, recent (< 2 years old) key reviews were marked and cross-checked

Studies identified during the gray literature search were excluded unless they came from Australia, Brazil, Canada, China, France, Germany, India, Italy, Japan, Korea, Russia, Spain, Turkey, the UK or the USA

Clinical efficacy and safety studies in relation to biologic switching

Clinical safety studies with only discontinuation data related to adverse events

Studies only reporting the number of patients who switched/discontinued biologic treatment

AS ankylosing spondylitis, *axSpA* axial spondyloarthritis, *CD* Crohn's disease, *JAK* janus kinase, *JIA* juvenile idiopathic arthritis, *MOA* mechanism of action, *nr-axSpA* non-radiographic axSpA, *PsA* psoriatic arthritis, *PsO* psoriasis, *RA* rheumatoid arthritis, *RCT* randomized controlled trial, *RWE* real-world evidence, *TNFi* tumor necrosis factor inhibitor

Table 2 Summary of compliance rates with TNFi at 1 year reported across all identified studies, by geographic region

Country	Data source	Time point	Treatment			
			Adalimumab	Etanercept	Infliximab	Golimumab
USA	Registries	1 year [82]	–	–	65.7% (CD)	–
	Claims data	1 year [50, 81, 99]	70.0%[a] (RA)	32%[a] (RA)	43%[a] (RA)	81.2[a] (RA)
				61.2%[a] (RA)	73% (CD)	
	Medical records	1 year [100]	–	–	96% (CD)[b]	–

The data included in the table include the results from studies reporting data from 1 through 7 years of anti-TNF use. Supplementary Table 1 provides a full list of studies identified, including those reporting values from 0–1 year

CD Crohn's disease, *RA* rheumatoid arthritis

[a] Based on proportion of days covered (PDC) ≥ 0.80

[b] Based on 4% appointments classified as 'no show'

Compliance with TNFi Therapy

Nineteen studies were identified reporting compliance data (summarized in Supplementary Table S1). The studies identified covered RA and CD patients treated with infliximab, adalimumab, golimumab or etanercept. Of these studies, 13 were conducted in the US and used data from large administrative claims databases. A summary of the reported compliance results over 1 year is provided in Table 2.

The methodology used to calculate compliance also differed across studies, which may have contributed to the variable results observed. Seven studies assessed compliance using the MPR or PDC by medication during the follow-up period [39, 41, 48–51], 1 assessed MPR using a fixed interval (365 days) as a denominator [41], and 2 studies used total days' supply of the medication as numerator and total days in the study period as denominator [39]. Compliance rates from studies using the MPR ranged from 52%, when MPR was calculated using total number of days of medication supply divided by total number of days in the study period, to 88%, when calculated by summing the days' supply value of the index treatment and dividing this amount by the sum of days between the index date and the most recent index treatment fill plus the days' supply value of the last fill.

No studies were identified comparing compliance rates between TNFi-naïve and TNFi-experienced patients, and no clear trends in treatment compliance over time were identified.

Persistence with TNFi Therapy

Only 53/110 identified studies reporting persistence described the methods used to define persistence. These included studies using large administrative claims databases and registries, which generally provided definitions and methodology for analyzing treatment persistence. Of the studies that did provide this information, there was significant heterogeneity in the methods used. For example, non-persistence was calculated using a variety of thresholds to measure the treatment gap (i.e., the number of days a patient had to be off therapy after exhausting their supply of drug): 13 studies used a > 90-day treatment gap after a biologic prescription was exhausted [17–29], 6 studies used a > 60-day treatment gap [30–35], 3 studies used a > 45-day treatment gap [36–38], and 3 studies used a > 30-day treatment gap [39–41].

Approximately two-thirds (75/110) of studies reporting persistence data used administrative databases or registries. In Europe, persistence data were often reported from large registry-based analyses; rates were generally shown to be highest in the UK and France, and lowest in Nordic countries, and ranged from 70–86% at 1 year of treatment [23, 42]. In the US, data were more often from large administrative claims databases and persistence rates were lower, ranging from 46–73% at 1 year (Table 3) [43–46].

Generally, the rates of persistence were higher in biologic-naïve patients, and there was no clear evidence to suggest a difference

Table 3 Summary of persistence rates with TNFi between 1 and 7 years reported across all identified studies, by geographic region

Country	Data source	Time point	Treatment				
			Adalimumab	Certolizumab pegol	Etanercept	Infliximab	Golimumab
Austria	Claims	1 year [46]	70% (AS)	–	83% (AS)	71% (AS)	–
		2 years [46]	55% (AS)	–	58% (AS)	54% (AS)	–
Belgium	Registries	5 years [89]	–	–	–	–	–
	Medical records	7 years [42]	–	–	–	36% (RA)	–
Denmark	Registries	1 year [19, 26, 44, 90]	–	–	73% (RA)	71% (RA)	–
						58% (PsA)	
Finland	Medical records	1 year [66]	–	–	83% (JIA)	80% (JIA)	–
		2 years [66]	–	–	68% (JIA)	68% (JIA)	–
		4 years [66]	–	–	61% (JIA)	48% (JIA)	–
France	Medical records	1 year [91, 92]	86% (RA)	–	87% (RA)	68% (RA)	–
			68.2% (RA and SpA)		76% (AS)	78.9% (AS)	
					63.9% (RA and SpA)	63.2% (RA and SpA)	
		2 years [91, 92]	66% (RA)	–	68% (RA)	46% (RA)	–
			60.2% (RA and SpA)		50.8% (RA and SpA)	83% (AS)	
						47.5% (RA and SpA)	
		50 months [91]	–	–	50% (RA)	–	–
Greece	Registries	1 year	67% (RA)	–	68% (RA)	64% (RA)	–
		5 years	43% (RA)	–	49% (RA)	31% (RA)	–
	Medical records	1 year [93]	83.7% (RA)	–	70% (RA)	82.9–84.5% (RA)	–
		5 years [45, 93]	44.9% (RA)	–	76% (PsA)	56.7% (PsA)	–
			50% (PsA)				
		7 years [93]	–	–	–	32.9% (RA)	–

Table 3 continued

Country	Data source	Time point	Adalimumab	Certolizumab pegol	Etanercept	Infliximab	Golimumab
Iceland	Registries	1 year [26]	–	–	–	66% (PsA)	–
Italy	Registries	3 years [94]	–	–	–	58% (RA)	–
	Registries	4 years [95]	36.4% (RA)	–	51% (RA)	37.6% (RA)	–
		5 years [94]	–	–	–	41.1% (RA)	–
	Medical records	1 year [24, 96]	65.38% (PsO)	–	65.65% (PsO)	71.43% (PsO)	–
			79% (RA)		76% (RA)		
		2 years [24, 96]	46.55% (PsO)	–	37.07% (PsO)	46.07% (PsO)	–
			60% (RA)		61% (RA)		
		4 years [96]	27% (RA)	–	21% (RA)	–	–
Japan	Registries	1 year [97]	–	–	84.6% (RA)	–	–
		2 years [54]	–	–	72% (RA)	–	–
		3 years [54]	–	–	67% (RA)	–	–
	Medical records	1 year [98]	78.2% (RA)	–	85.9% (RA)	73.1% (RA)	–
		2.5 years [98]	54.5% (RA)	–	77.7% (RA)	47.2% (RA)	–
		5 years [98]	–	–	61.9% (RA)	29.8% (RA)	–
The Netherlands	Registries	1 year [27]	74% (PsO)	–	68% (PsO)	–	–
Spain	Registries	1 year [68]	67–87% (RA, AS, PsA, JIA, etc.)	–	76–88% (RA, AS, PsA, JIA, etc.)	–	–

Table 3 continued

Country	Data source	Time point	Treatment				
			Adalimumab	Certolizumab pegol	Etanercept	Infliximab	Golimumab
Sweden	Registries	1 year [34]	57% (RA, PsA and AS)	55% (RA, PsA, AS)	56% (RA, PsA, AS)	–	58% (RA, PsA, AS)
		2 years [34]	40% (RA, PsA and AS)	40% (RA, PsA and AS)	39% (RA, PsA and AS)	–	46% (RA, PsA and AS)
		3 years [34]	33% (RA, PsA and AS)	33% (RA, PsA and AS)	33% (RA, PsA and AS)	–	40% (RA, PsA and AS)
Taiwan	Medical records	1 year [57]	83.3% (RA)	–	91.1% (RA)	–	–
UK	Registries	1 year [22]	91% (PsA)	–	86% (PsA)	71% (PsA)	–
		2 years [22]	70% (PsA)	–	79% (PsA)	52% (PsA)	–
		3 years [22]	66% (PsA)	–	65% (PsA)	43% (PsA)	–
USA	Claims	1 year [32, 36, 38]	47% (RA, PsO, PsA and AS)	–	42% (RA, PsO, PsA and AS)	56% (RA, PsO, PsA and AS)	–
			45% (PsA)		50% (PsA)	68.9-96.4% (RA)	
			66-94% (RA)		62.2-89.2% (RA)		

The data included in the table include the results from studies reporting data from 1 through 7 years of anti-TNF use. Supplementary Table 1 provides a full list of studies identified, including those reporting values from 0–1 year

AS ankylosing spondylitis, *JIA* juvenile idiopathic arthritis, *PsA* psoriatic arthritis, *PsO* psoriasis, *RA* rheumatoid arthritis, *SpA* spondyloarthritis

between switching within class (i.e., to another TNFi) or switching to a biologic with a different mechanism of action [47].

Factors Leading to Suboptimal Persistence and Compliance

Cox regression modeling has been used in a number of studies to identify factors that may predict rates of treatment persistence. A variety of factors were identified as potentially predictive of suboptimal treatment persistence. These included increased age, female gender, presence of a comorbidity, high disease activity at diagnosis, longer disease duration, smoking, increased body mass index, higher treatment dose, higher treatment cost and lower HRQoL scores [17–20, 22, 26, 28, 39, 52–72]. Several studies have identified a variety of patient-reported reasons for non-compliance and non-persistence. Reasons have included forgetfulness, intentional non-compliance, supply issues, patient misunderstanding of their treatment regimen, medication ineffectiveness, cost/affordability of treatment, a lack of motivation or social support, fear of self-injection and reduced hand dexterity [12, 15, 73–75].

Impact of Drug Delivery Devices and Patient Support Services on Compliance and Persistence

Patients often cited factors associated with medication delivery as a reason for non-compliance and non-persistence. Four studies utilizing various methodologies examined the effect of treatment self-administration with various delivery devices on compliance and persistence (Table 4), reporting results indicating that self-injection devices may offer solutions to some of the reasons for non-compliance and non-persistence.

Switching from a prefilled syringe to an auto-injector was associated with improved treatment compliance and persistence; patients with chronic diseases reported that auto-injection devices were preferable over prefilled syringes because they were less painful and simpler to use [74, 76, 77]. In one study, a 30% increase was observed in the number of patients self-administrating medication after switching to an auto-injector, which in turn led to a decrease in the proportion of patients requiring outpatient visits or additional assistance [76]. Two single-center studies reported similar results in patients switching from a prefilled syringe to an auto-injection pen; the first enrolled 55 patients and demonstrated 100% persistence with an adalimumab auto-injection pen over 8 weeks, while the second enrolled 104 patients and demonstrated > 95% compliance with an etanercept auto-injection pen over 8 weeks [74, 76]. Similar results were also seen with golimumab. The GO-MORE trial, reporting the use of the GOL SmartJect® (Janssen Biotech Inc, Horsham, PA, USA) auto-injection device in RA patients, reported that high persistence and compliance were maintained throughout the study, with 91.7% of patients completing 6 months of treatment and > 80% of patients adhering to the recommended monthly dosing frequency [77].

One paper was identified highlighting the benefits of patient support services on treatment compliance (Table 4). The study described the impact of patient enrollment on myHUMIRA® (AbbVie, North Chicago, IL, USA) patient support program (PSP) and indicated that patients enrolled in the PSP showed greater intent to comply with treatment, had higher treatment satisfaction and had greater perception of treatment benefits. However, it must be noted that patients enrolled voluntarily in the PSP; thus, compliance results are likely to be more favorable [78]. No studies reporting the impact of patient support services on treatment persistence with TNFi therapy were found during the review.

Clinical and Economic Consequences of Treatment Non-Compliance and Non-Persistence

Patient non-compliance and non-persistence have been shown to have a significant impact on treatment outcomes from both a clinical and economic perspective. Suboptimal treatment compliance and persistence are associated with increased morbidity and mortality, as well as suboptimal outcomes in terms of treatment

Table 4 Key findings on treatment self-administration with treatment devices on treatment persistence and compliance

Study	Patients	Type of device	Key outcome
Treatment devices			
Borrás-Blasco [76]	Phase 1: $N = 55$ (RA: 29, PsA: 17, AS: 9) Phase 2: $N = 51$ (4 lost)	Adalimumab: Prefilled syringe vs. auto-injection pen	Patients reported 100% adherence to treatment with the auto-injection pen over an 8-week period
Borrás-Blasco [74]	RA, PsA, AS patients Phase 1: $N = 82$ Phase 2: $N = 104$	Etanercept: Prefilled syringe vs. auto-injection pen	Patients reported > 95% adherence to treatment with the etanercept auto-injection pen over an 8-week period
Calip [101]	$N = 53,477$ (etanercept: 26,996; adalimumab: 22,210; certolizumab pegol: 1601; golimumab: 2670)	Mixed injection devices, self-administered	Compliant: year 1 (36.5%), year 2 (33.6%), year 3 (28.8%) Persistent: year 1 (82.6%), year 2 (80.5%), year 3 (80.1%)
Schulze-Koops [77]	RA ($N = 3280$)	Golimumab (SmartJect® auto-injection device) (Janssen Biotech Inc, Horsham, PA, USA)	91.7% completed 6 months of treatment
Patient support services			
Liu et al. [78]	Responder, patients receiving adalimumab: ($N = 299$) RA (36%), CD (24%), PsO (22%), PsA (22%), UC (9%), AS (7%)	Adalimumab (myHUMIRA®) (AbbVie, North Chicago, IL, USA) PSP	Patients in PSP vs. non-PSP: Intention to be non-compliant: 3.6 vs. 3.2 ($p < 0.001$) Therapy satisfaction: 4.1 vs. 3.5 ($p < 0.001$) Perception of therapy as beneficial: 3.6 vs. 3.2 ($p < 0.001$)

AS ankylosing spondylitis, *CD* Crohn's disease, *PsA* psoriatic arthritis, *PsO* psoriasis, *PSP* patient support program, *RA* rheumatoid arthritis, *UC* ulcerative colitis

benefit and symptomatic improvement. In turn, this leads to higher healthcare costs and more frequent outpatient visits [10, 14].

Multiple studies identified during the review indicated that suboptimal persistence and compliance were associated with lower clinical effectiveness (Table 5). For example, one study demonstrated that RA patients who received TNFi, and had higher persistence rates, had significantly lower disease activity scores (DAS [28]) than those with lower persistence rates [79]. Another study demonstrated that high compliance rates were associated with a greater reduction in DAS28 scores over 6 months of subcutaneous TNFi therapy [80].

Overall, evidence suggests that suboptimal compliance and persistence are associated with higher costs and increased burden on healthcare services (Table 5). In studies of patients with CD, suboptimal compliance was found to be associated with significantly higher rates of hospitalization and surgery, more emergency room visits, significantly longer hospital stays and higher healthcare costs in comparison with compliant patients [81–83]. A Swedish retrospective registry study demonstrated that the healthcare resource utilization cost in AS, PsA and RA non-persistent patients was higher following a period of treatment non-persistence

Table 5 Overview of studies on clinical and economic implications of suboptimal treatment persistence and compliance

Study	Type of study	Data source, country	Clinical and/or economic implications	Compliance	Persistence
An [102]	Multicenter observational cross-sectional study	Questionnaire China	A significantly larger proportion of patients with ≥ 12 months bDMARD therapy achieved treatment target (low disease activity or remission) compared with patients with < 12 months		X
			Proportion of patients achieving treatment target was significantly lower in patients with < 3 months bDMARDs with 3.0–5.9 months bDMARDs		
Billioud [73]	Observational multicenter study (medical records from 4 university hospitals)	France	Predictors of non-compliance include having at least one relapse in the past 12 months, having a disease duration over 93 months, and receiving adalimumab 80 mg every other week (two injections at once)	X	
			The main reasons for delay were forgetfulness, travel and infection		
Borah [41]	Retrospective cohort analysis	Claim data USA	Among non-compliant patients, the number of inpatient visits was significantly higher for etanercept users vs. adalimumab users	X	
			Etanercept users had significantly lower RA-related pharmacy costs and RA-related total costs than adalimumab users		
Bluett [80]	Multicenter prospective observational cohort study (Biologics in RA Genetics and Genomics Study Syndicate study)	UK	Non-adherence was significantly associated with a lower DAS28 response following 6 months of subcutaneous TNFi therapy	X	

Table 5 continued

Study	Type of study	Data source, country	Clinical and/or economic implications	Compliance	Persistence
Carter [81]	Retrospective observational study	IMS PharMetrics database USA	Mean hospital costs were significantly lower for compliant patients vs. non-compliant patients, with compliant patients requiring fewer emergency room visits and less hospitalization Among those hospitalized, compliant patients spent fewer days in the hospital vs. non-compliant patients	X	
Courvoisier [103]	Cross-sectional multicenter study	Registries Sweden, Czech Republic, Denmark, Italy, Norway, France Portugal, Canada, Switzerland	Proportion of patients with EULAR good or moderate response rate (Lundex corrected) at 1 year was higher among 'rapid responders'		X
Dalen [34]	Retrospective observational study	Swedish Prescribed Drug Register Sweden	Mean total costs prior to and post-treatment initiation decreased in persistent patients, and increased in non-persistent patients		X
Degli Esposti [86]	Observational retrospective cohort	3 databases of Italian Local Health Authorities Italy	The treatment costs for patients switching from initial treatment during the first year of follow-up were higher than for patients who did not switch (€12,710 vs. €11,332) For patients not persistent with their initial drug, other healthcare costs (hospitalizations, specialist care, etc.) were significantly higher than those for persistent patients (€1,088 vs. €375)		X

Table 5 continued

Study	Type of study	Data source, country	Clinical and/or economic implications	Compliance	Persistence
Foster [104]	Retrospective observational cohort study	MarketScan claims database USA	Total healthcare costs were lower in non-treatment-regimen failures than in treatment-regimen failures ($6,637 vs. $8,024; $p = 0.002$) Psoriasis-related total healthcare costs were higher in non-treatment-regimen failures than in treatment-regimen failures ($25,286 vs. $19,625; $p < 0.001$)		X
Harnett [84]	Retrospective cohort analysis	Truven Marketscan, Commercial Claims and Encounters and Medicare Supplemental Databases USA	Discontinuers had significantly lower RA-related costs compared with those classified as switchers		X
Inzinger [105]	Observational retrospective multicenter study	Psoriasis Registry Austria	Drug survival correlated significantly with effectiveness for adalimumab and etanercept, but not for infliximab		X
Kane [82]	Observational study	Integrated Health Care Information Service (IHCIS) National Managed Care Benchmark Database USA	Adjusted medical and hospitalization costs for non-compliant patients were greater compared with compliant patients Etanercept had the lowest 1-year index biologic cost per effectively treated patient, followed by adalimumab, infliximab, abatacept, and rituximab	X	

Table 5 continued

Study	Type of study	Data source, country	Clinical and/or economic implications	Compliance	Persistence
Lequerre [106]	Observational retrospective cohort	France	A greater proportion of patients were considered responders (DAS28 improvement > 1.2) after the second biologic agent ($p < 0.01$) DAS28 improvements were more pronounced with the second immunotherapy than the first ($p < 0.001$), regardless of type of failure or switching order		X
Sauer [107]	Observational retrospective cohort	Corporate Data Warehouse USA	Among the patients categorized as ineffectively treated, the most common criterion for failure was low adherence, followed by addition of a new DMARD, having a new or increased oral glucocorticoid dose, switching biologics, increasing the biologic dose and having > 1 glucocorticoid injection	X	
Stein [83]	Retrospective observational study	Medical records USA	The prior irregular group (no loading, gap in therapy > 8 weeks prior to or during maintenance infliximab) showed higher rates of hospitalizations and surgical hospitalizations compared with the scheduled maintenance group (maintenance infliximab infusions every ≤ 8 weeks after loading dose) at Year 3 The prior irregular group had higher excess costs per patient during the 3rd year of infliximab maintenance therapy, despite both groups receiving scheduled maintenance therapy		X

Table 5 continued

Study	Type of study	Data source, country	Clinical and/or economic implications	Compliance	Persistence
Svedbom [108]	Retrospective administrative register study	Registries Sweden	In patients who remained persistent with treatment for at least 6 months, the annualized costs incurred with first-line TNFi were lower than costs incurred with second-line TNFi		X
			During this period, mean TNFi costs were lower in second-line patients compared with first-line patients		
			Excluding TNFi costs, there was no statistically significant difference in costs between first- and second-line patients in the 6 months preceding indexation		
Tang [85]	Retrospective observational study	IMS PharMetrics database USA	The > 80% persistence cohort had higher total healthcare costs, driven by higher pharmacy costs		X
			The > 80% persistence cohort had lower medical (non-pharmacy) healthcare costs		

bDMARD biologic disease-modifying antirheumatic drug, *DMARD* disease-modifying antirheumatic drug, *EULAR* European League Against Rheumatism, *RA* rheumatoid arthritis, *TNFi* tumor necrosis factor inhibitor

than at the start of therapy, whereas reduced healthcare resource costs were seen in persistent patients [34].

During first-line biologic treatment, non-persistent patients with RA had significantly higher healthcare costs (hospitalizations, specialist care, etc.); patients undergoing a treatment switch to a second TNFi following a failure to respond to the first incurred the highest 1-year total healthcare costs, and the treatment costs for patients switching from the initial treatment during the first year of follow-up were higher than for patients who did not switch [84]. When comparing switching to another TNFi as opposed to switching out of class, all-cause costs were higher in patients switching to

a non-TNFi biologic DMARD compared with an alternative biologic TNFi [84]. Overall, RA patients with high rates of persistence (> 80%) had higher total healthcare costs, driven by higher pharmacy costs; however, the total non-pharmacy costs, including in- and outpatient visits and laboratory services, were lower than costs reported for patients with persistence rates of < 80% (Table 5) [85, 86].

DISCUSSION

This targeted literature review examined treatment compliance and persistence and their drivers in patients undergoing biologic

treatment across a number of CIDs to understand the role of different treatment-related factors and the potential consequences of suboptimal compliance and persistence. In the majority of studies, the terms compliance and persistence were mixed without adequate description of the methodology used in the analyses, making interpretation of the results very difficult. In studies that did describe the methodology, notable heterogeneity in the methods used to measure treatment persistence and compliance was identified. Furthermore, the data sources used varied significantly from study to study and were often associated with specific limitations or biases. For example, registries were reliant on doctors' notes that were based on patient self-reported data on drug intake, prescription data did not necessarily take into account the doctor-prescribed dose, and studies where patients were recruited from routine clinical practice generally had a small sample size with low geographic representativeness.

When looking at geographic patterns, persistence rates to prescribed biologics were higher in the UK and France than in Nordic countries, and EU studies generally reported higher rates than US studies. Within the EU, there are variations between country guidelines for the management of CIDs, for example, the approach to dose optimization and tapering differs from country to country. Differences also exist in the local availability of biologics and in the type of practice or specialist (e.g., dermatologist, gastroenterologist or rheumatologist) prescribing treatments for these indications, which may explain some of the differences observed between countries. The lower levels of compliance and persistence reported in the US compared with the EU may be, in part, due to the lack of a national health insurance scheme in the US as well as due to the key differences in data sources and data collection methods.

The review also identified papers showing that patients who cycle through multiple biologic therapies incur higher costs and become less responsive to treatment [84, 86]. Therefore, in the context of chronic diseases, it is beneficial to both individual patients and health systems

to optimize patient journeys to ensure patients can cope with their treatment and remain compliant and persistent so as to avoid frequent cycling of multiple treatment options.

Both qualitative and quantitative research methods were used to assess the impact of devices on compliance and persistence; no standard questionnaire or measurement was used to evaluate the device usability and acceptability, patients' preferences and treatment satisfaction. These limitations made it challenging to synthesize data in an informative way, so it is difficult to review the general treatment experience and impact of treatment devices on compliance and persistence. Despite these challenges, this review identified a number of factors associated with treatment delivery that appear to influence compliance and persistence and so represent possible targets for future interventions. For example, a number of studies reported improvements in compliance and persistence following changes to the delivery device. Interventions, such as easing the route of medication administration through the use of auto-injection pen devices, providing support to patients to ensure they are able make informed decisions about their device choice to ensure it meets their specific needs, and device design improvements such as dose reminder functions were all associated with high compliance and persistence rates. General patterns were observed suggesting treatment non-compliance and non-persistence were associated with poorer clinical outcomes and higher treatment and healthcare costs, and compliant patients tended to experience fewer clinical events. However, this may be due to underlying differences in patients' disease severity and comorbidities, which may confound the effect of non-compliance on outcomes.

While this review highlighted that compliance and persistence represent two key areas that, if improved, would positively impact treatment outcomes, there were several limitations. The aim of this review was to provide a broad overview of biologic therapy so a targeted approach was used to identify real-world studies reporting compliance and persistence data. Consequently, it is possible that studies may have been missed; however, as the

heterogeneity of data reported within the literature limits any comparison of compliance and persistence between studies, it is unlikely that including any additional studies would impact the conclusions of this review. The majority of studies focused on treatment of patients with RA or AS using the conventional biologics, etanercept, adalimumab and infliximab, so may not be truly representative of treatment across other CIDs. Prescription orders from doctors are often unavailable in the databases used to calculate compliance, and so the reported rates may not take into account alternative dose regimens (in- or off-label). Therefore, compliance estimates are often blinded to dose escalation or dose down-tapering. Although this is unlikely to impact the results from patients starting treatment, they are common practices in these conditions and thus important determining factors [7, 8, 87]. Finally, data used to calculate compliance are mainly self-reported by patients and so are subject to self-reporting bias.

The results of this review clearly demonstrate that non-compliance and non-persistence are important public health considerations that affect the success of therapeutic treatment, disease remission and disease severity [88]. To understand what interventions can influence compliance and persistence, the methods used to report these measures first need to be aligned; without consistency in the methods and definitions used, it is difficult to draw comparisons between studies to fully understand patients' reasons for non-compliance and non-persistence or understand individual barriers to optimal treatment use. Gaining a complete understanding of the intentional and unintentional causes driving non-compliance and non-persistence in individual patients will enable tailored solutions, such as improved devices, services and patient support interventions, to be developed to tackle each of these barriers. As persistence and compliance with biologic therapies have the potential to reduce the treatment costs and improve patients' clinical outcomes and quality of life, this is an important area for future research.

CONCLUSIONS

Biologic therapy non-compliance and non-persistence have implications for both clinical and economic outcomes. A variety of factors contributing to treatment compliance and persistence were identified during this review of the available literature, and this evidence should be used to develop solutions to improve disease management and optimize treatment regimens. Tailoring treatment delivery devices and patient support services has the potential to improve compliance and persistence and so represents an important area for future research. This has the potential to benefit patients' health by improving clinical outcomes and reducing the burden to society by limiting the economic impact of patients' disease.

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