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PHARMACOEPIDEMIOLOGY

Characterization of adherence and persistence profile in a real-life population of patients treated with adalimumab

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AIMS

Published data on long-term adherence and persistence with adalimumab (Humira®) in clinical practice are scarce and often limited to selected patient populations. This study assessed adherence with adalimumab across different indications and identified correlates and outcomes of poor adherence.

METHODS

We analysed data originating from the electronic database of Maccabi Healthcare Services (MHS) that includes 2.1 million enrolees. We randomly selected patients with at least one dispense of adalimumab since it was included in the local health basket in Israel in 2008 until the end of 2013. Patients with the following indications (n = 1339) were included: Crohn's disease (CD), ulcerative colitis (UC), rheumatoid arthritis (RA), psoriatic arthritis (PSA), ankylosing spondylitis (AS) and psoriasis. Adherence with therapy was assessed by the medication possession ratio (MPR) during the follow-up period.

RESULTS

Good adherence (MPR ≥ 80%) was observed among 80% of study patients and was associated with lower risk for ≥1 hospitalization per year of follow-up (adjusted-OR = 1.94, 95% CI:1.15–3.28). Patients with AS and CD persisted on adalimumab therapy the most, reaching median use of 27.0 and 26.7 months, respectively. Half (52.4%) of the patients discontinued treatment during a mean (SD) follow-up of 3.07 (1.71) years. High socioeconomic status was associated with lower risk for discontinuation (adjusted-HR = 0.74; 0.60–0.91). UC and concomitant prednisolone use were associated with increased risk for treatment discontinuation (HR = 1.31; 1.00–1.72, and HR = 1.40; 1.17–1.68, respectively).

CONCLUSION

Our results indicate encouraging persistence and adherence with adalimumab of patients with inflammatory conditions.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- 'Real life' studies across different medical disciplines show poor adherence rates to drug therapy.
- Many studies have shown that low adherence rates to therapy results in overall poor clinical outcomes. This pattern has also been demonstrated in multiple rheumatic conditions.

WHAT THIS STUDY ADDS

- The vast majority of patients with different inflammatory conditions show extremely high rates of adherence to therapy with adalimumab (Humira) reaching rates above 80%.
- Higher rates of adherence were associated with lower rates of hospitalizations in patients treated with adalimumab (Humira).

Introduction

Immune-mediated inflammatory disorders include a large group of conditions of unknown aetiology that are clinically diverse. They affect millions of people worldwide, including 5–7% of the population of Western societies. These patients have various comorbidities, which strongly impact their quality of life and longevity [1–7].

Despite their clinical heterogeneity, many of these immune-mediated disorders share common inflammatory pathways, which trigger dysregulation of the normal immune response [8–11]. Tumour necrosis factor-alpha (TNF-α) serves as a key regulator of innate immunity and plays an important role in the regulation of Th1 immune responses against microbiological pathogens. However, dysregulated TNF-α can also contribute to numerous pathological conditions. This discovery heralded a new era of targeted and highly effective therapies for rheumatoid arthritis (RA) and subsequently for other chronic inflammatory disorders such as inflammatory bowel disease (IBD), psoriasis and spondyloarthopathies.

Anti-TNF agents, either in the form of a neutralizing monoclonal antibody or as a soluble TNF receptor blocker, induce biological and cellular mechanisms that revolutionized the clinical management of these inflammatory disorders [12–14]. Treatment with anti-TNF medications brought about significant therapeutic improvements in many prospective studies and randomized control trials (RCTs) for several immune-mediated conditions [1, 10, 12, 13]. Nevertheless, the successful results observed in RCTs are usually achieved with a high degree of medication adherence, not necessarily representing real-world patients' behaviour.

Treatment adherence, defined as the extent to which patients take medications prescribed by their healthcare providers, depends on many factors including the type of medication, concomitant drug use and familial and medical support [15, 16].

Several factors affect the levels of compliance with biological therapy in Israel that differentiate them from other medications. The co-payment of the patients ('out of pocket' costs) is not negligible, and is about $75 a month. Given the high costs and profits of biological therapy, in order to preserve high adherence rates, all the pharmaceutical companies hire nurses that are in continuous contact with the patients either directly or by a third party (dependent on the company's regulations). By and large, in Israel, patients are instructed to self-administer the medication, yet a minority of them seeks the assistance of nurses in the communities' clinics or of family members.

The parenteral mode of administration also impacts adherence rates; the fact that the medication is injected subcutaneously mandates periodical encounters with health professionals even in the case of self-use. This, by nature, improves the persistence and adherence rates. Mohr *et al*. [17] have found that for injectable treatments, self-administration is associated with better compliance than when given by healthcare providers and family members. Previous adherence studies in different indications such as gout and fibromyalgia have also found that single individuals are less adherent than those who live with family members [15, 16, 18].

Any deviation from the prescribed drug regimen may lead to treatment failure and disease or symptom recurrence, as well as increased healthcare costs [19]. A large multicentre, prospective, observational cohort study of RA patients in the UK found that inadequate adherence to biologics resulted in worse clinical outcomes compared to those of adherent counterparts [20]. A retrospective study based on an American healthcare database of Crohn's disease patients showed that low adherence to **adalimumab** treatment was associated with increased medical costs and hospitalizations [21].

The definitions of 'adherent' and 'non-adherent' and methods for measuring adherence lack consensus [15, 22]. A recent systematic review of over 20 studies [23] analysing adherence to biologic therapies and associated factors for a variety of inflammatory conditions reported diverse results across studies. This was partially due to the wide variability in the definition of adherence, study design and measurement methods.

The current research characterized and evaluated adherence and persistence with adalimumab treatment, which is the first fully human monoclonal antibody directed against TNFα. It is given subcutaneously once every two weeks for a broad variety of immune-mediated disorders. Our study investigated the factors associated with compliance of a 'real-life' population of patients with a variety of immune-mediated inflammatory conditions.

Methods

Study sample and data collection

We conducted a retrospective cohort study using the database of Maccabi Healthcare Services (MHS); the second largest

healthcare provider in Israel. The MHS patient database is contained within a central electronic medical record system, with over 18 years of longitudinal data on a stable population of approximately 2.1 million people. We received the approval of the MHS ethics board to conduct this study (approval number (36/2013).

The study sample comprised a stratified, random sample of all patients in the database with at least one dispense of adalimumab between 1 January 2008, the date of its inclusion in the national dispensary in Israel, and 31 December 2013. Patients were stratified according to the disease for which adalimumab was prescribed, defined as the last relevant diagnosis reported in the medical record prior to first dispense. Within each stratum, the sample size was randomly determined within a fixed interval of 100–350 patients (to accommodate MHS policy of confidentiality regarding the numbers of patient per indications). Patients were then randomly selected for the study. Diseases included Crohn's disease (CD), ulcerative colitis (UC), RA, psoriatic arthritis (PSA), ankylosing spondylitis (AS), and psoriasis. Since juvenile idiopathic arthritis was included in covered health services only in 2010, the total number of patients with dispensed adalimumab was low. Thus, this indication was not included in the study. Date of first dispense of adalimumab was defined as the index date. Follow-up concluded on 31 December 2013.

Using the patients' unique 9-digit national identification numbers, data extracted from the database included demographics (age, sex, district of residence and date of immigration), BMI, smoking status, medication dispenses, visits to primary and secondary clinics, and hospitalization dates. Disease information was also extracted from MHS automated patient registries, including diabetes mellitus, chronic kidney disease (CKD), hypertension (HTN), cancer, and cardiovascular disease registries. These registries are automatically updated daily according to strict computerized algorithms [24, 25]. Concomitant pharmacological treatments were defined as at least two dispenses within 180 days from the index date and included **azathioprine**, methotrexate, **hydroxychloroquine**, **sulfasalazine**, **leflunomide**, mercapto-purine and prednisone. Patients with less than 90 days of follow-up or less than 1 year enrolment in MHS prior to first dispense of adalimumab were excluded (Figure 1).

Socioeconomic status (SES) was defined according to the poverty index of the member's enumeration area, as defined during the Israeli national census in 2008. The poverty index is based on several parameters, including household income, education, crowding, material conditions, and car ownership. It ranges from 1 to 20, based on cluster analysis, with 1 being the lowest and 20 being the highest SES level [26].

Compliance with treatment

We evaluated adherence with medical therapy using the Medication Possession Ratio (MPR), which reflects the ratio of the number of treatment days dispensed and the total number of days from first dispense to the last supply day of the last dispense in the follow-up period or until discontinuation of 180 days or more. Patients were followed until 31 December 2013; however, an additional 180 days were assessed for dispenses of adalimumab to allow for evaluation

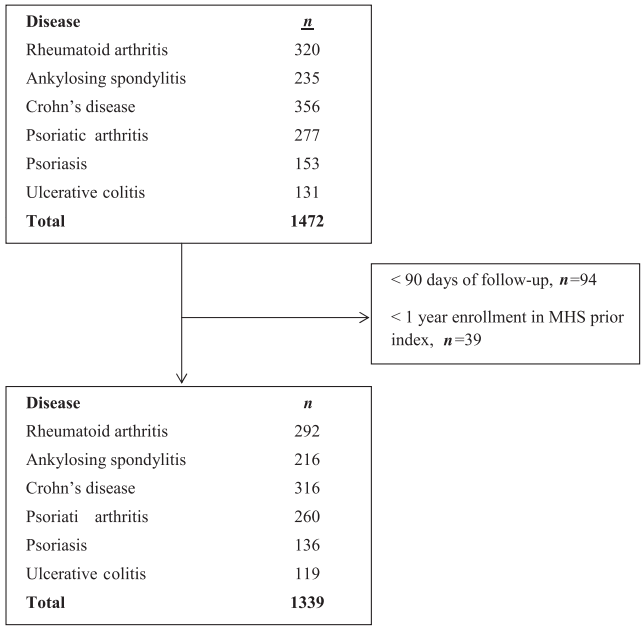

Figure 1

Disposition of patients throughout the study phases. Patients with <90 days of follow-up or <1 year enrolment in MHS prior first dispense of adalimumab were excluded

of gap in treatment of 180 days or more for all study patients. Adherence was defined as high (MPR ≥ 80%), intermediate (20% < MPR < 80%) or low (MPR < 20%), or as a dichotomous variable, MPR ≥80% (adherent) vs. MPR <80% (non-adherent). Persistence was measured by the duration from initiation to discontinuation of therapy, defined as a gap of 180 days or more between dispenses. Concomitant use of methotrexate among RA patients was also assessed. This was defined as at least two dispenses (one in the 180 days before and one following the first dispense of adalimumab). It should be underlined that even in the event of patients who chose to be injected by a health professional, it remained their responsibility to dispense the medications. Therefore, the mode of administration did not affect the adherence or persistence rates that were investigated in this study.

Statistical analysis

Mean ± standard deviation (SD) or medians ± inter-quantile range (IQR) and proportions were calculated for continuous and categorical variables, respectively. Continuous baseline patient characteristics were compared between study groups using the Mann–Whitney or Kruskal–Wallis test, as appropriate. Categorical characteristics and MPR levels were compared using the Chi-square test. Correlation between categorical variables was assessed using the Spearman correlation coefficient. Kaplan–Meier methods were used to construct disease-specific curves for time to treatment discontinuation and the log-rank test was used to evaluate statistical significance. Multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for time to

treatment discontinuation. The proportional hazards assumption was examined visually using Schoenfeld residuals plotted over time, and found to be reasonably fulfilled for all covariates. Multivariate logistics regression models were used to estimate odds ratios (OR) and 95% CIs for factors associated with adherence (MPR ≥ 80%) vs. non-adherence (MPR < 80%). In addition, various measures of health services utilization during follow-up were compared between adherent and non-adherent patients using multivariate logistic regression models, for dichotomous measures, and multivariate generalized linear models with gamma distribution and log-link function, for continuous measures. Selection of covariates for inclusion in all final regression models was based on the minimal Akaike information criterion and clinical relevance. In sensitivity analysis, only patients with at least 2 years of follow-up were analysed. Analyses were done using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp, Armonk, NY).

Table 1

Characteristics of study patients by indication (n = 1339)

Characteristic	RA (n = 292) % (n)	AS (n = 216) % (n)	CD (n = 316) % (n)	PsA (n = 260) % (n)	Psoriasis (n = 136) % (n)	UC (n = 119) % (n)	Total (n = 1339) % (n)	P-value
Age (mean, SD)	53.0 (14.4)	36.1 (15.4)	41.7 (14.2)	47.6 (12.7)	33.7 (12.8)	44.1 (11.5)	43.3 (15.1)	<0.001
Female sex	81.2% (237)	34.3% (74)	50.9% (161)	53.8% (140)	38.2% (52)	55.5% (66)	54.5% (730)	<0.001
SES score (1–20 scale; mean, SD)	12.5 (4.0)	12.4 (4.1)	12.9 (4.1)	12.4 (4.2)	12.4 (4.4)	13.4 (3.7)	12.5 (4.0)	0.198
Missing SES score	12.3% (36)	13.4% (29)	17.4% (55)	15.8% (41)	13.2% (18)	16.8% (20)	14.9% (199)	0.513
District								
Centre	63.4% (185)	65.7% (142)	67.1% (212)	66.2% (172)	72.1% (98)	73.9% (88)	67.0% (897)	0.030
North	25.0% (73)	20.8% (45)	14.6% (46)	19.2% (50)	14.7% (20)	15.1% (18)	18.8% (252)	
South	11.6% (34)	13.4% (29)	18.4% (58)	14.6% (38)	13.2% (18)	10.9% (13)	14.2% (190)	
Ever smoked	20.5% (60)	23.6% (51)	19.0% (60)	16.2% (42)	23.5% (32)	18.5% (22)	19.9% (267)	
BMI (kg m^{-2})								
<25	18.2% (53)	14.4% (31)	44.9% (142)	14.2% (37)	14.7% (20)	36.1% (43)	24.3% (326)	<0.001
26–30	30.5% (89)	32.9% (71)	19.0% (60)	32.3% (84)	30.1% (41)	21.8% (26)	27.7% (371)	
>30	29.8% (87)	28.7% (62)	6.6% (21)	36.5% (95)	27.2% (37)	16.8% (20)	24.0% (322)	
Unknown	21.6% (63)	24.1% (52)	29.4% (93)	16.9% (44)	27.9% (38)	25.2% (30)	23.9% (320)	
Clinical history								
Cardiovascular disease	13.7% (40)	7.9% (17)	3.5% (11)	7.7% (20)	8.1% (11)	5.9% (7)	7.9% (106)	<0.001
Diabetes	11.3% (33)	6.5% (14)	2.5% (8)	16.5% (43)	9.6% (13)	7.6% (9)	9.0% (120)	<0.001
HTN	31.5% (92)	17.1% (37)	7.9% (25)	30.0% (78)	18.4% (25)	9.2% (11)	20.0% (268)	<0.001
CKD	12.7% (37)	6.0% (13)	3.2% (10)	6.5% (17)	5.1% (7)	5.0% (6)	6.7% (90)	<0.001
History of cancer	6.5% (19)	0.5% (1)	5.4% (17)	4.6% (12)	2.2% (3)	5.9% (7)	4.4% (59)	0.016
Utilization of healthcare services in baseline year, median (IQR)								
Primary care visits	22.5 (15–36)	17 (11–27)	20 (13–31)	18 (12–29)	13.5 (7.5–23)	28 (16–37)	20 (12–31)	<0.001
Secondary care visits	9 (5–14)	9 (5–13)	6 (2–10)	8 (4–14)	9 (4–13)	6 (2–13)	8 (4–13)	<0.001
≥1 Hospitalization	21.9% (64)	17.1% (37)	49.1% (155)	16.5% (43)	22.8% (31)	48.7% (58)	29.0% (388)	<0.001
Number of inpatient days among hospitalized patients (n = 388)	4.5 (2–10.5)	4 (2–9)	5 (2–10)	4 (1–9)	7 (4–16)	7 (4–12)	5 (2–11)	0.015

Crohn's disease (CD), ulcerative colitis (UC), rheumatoid arthritis (RA), psoriatic arthritis (pSA), ankylosing spondylitis (AS)

Nomenclature of targets and ligands

Key ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal fo data from the IUPHAR/BPS Guide to PHARMACOLOGY [27].

Results

A total of 1339 patients were followed for a mean (SD) of 3.07 (1.71) years. Ages ranged from 5.5 to 91.5 years. Patients with AS, psoriasis and CD were significantly younger than the others (Table 1). Most RA patients were female, while the majority of AS patients were male. In addition, more individuals who ever smoked were reported among patients with AS and psoriasis compared to other disorders. Lower BMI ratios were recorded among patients with IBD, while patients with psoriasis and psoriatic arthritis (PSA) had higher BMIs.

During the year prior to the day of inclusion in the study, patients with IBD were hospitalized more often compared to other patients, with almost half hospitalized at least once (Table 1). Except for psoriasis patients, of whom 65% had at least ten encounters with their primary care physician, 80–89% of patients in all other disease groups visited their primary-care physician ten or more times during the baseline year, with a median of >15 visits for most groups. In addition, 30–48% had at least ten encounters with a secondary-care physician with a median of 6–9 in the various groups.

Only half of RA patients who received adalimumab were also treated with methotrexate. Among RA patients given adalimumab, 42.1% were co-treated with prednisone. Lower, but significant percentages of UC and CD patients were treated with steroids during the first 6 months following the initiation of adalimumab (18.4% and 14.9%, respectively) (Supplementary Table S1). As expected, mercaptopurine was given primarily to patients with IBD (12% to patients with CD and 10.9% to those with UC).

Adherence to treatment

The MPR of adalimumab among patients of all inflammatory conditions analysed in this study was 80% or more in approximately 80% of the patients with no statistically significant differences between conditions (Figure 2). Patients with low compliance (MPR < 80%) were 2 years younger on average and had fewer visits to primary- and secondary-care clinics in the baseline year compared to those with high compliance (MPR ≥ 80%) (Table 2). Concomitant use of methotrexate was lower among patients with low vs. high MPR (13.5% vs. 21.7%, respectively, $P = 0.046$). After adjusting for age, sex, disease group, smoking status and length of follow-up, the association of age with high MPR remained significant (OR = 1.01 per 1-year increment, 95% CI: 1.00–1.03, $P = 0.012$). In addition, compared with RA patients, psoriatic arthritis patients were significantly less likely to be compliant (OR = 0.56; 0.33–0.97, $P = 0.038$). No other differences were observed between high and low compliant patients (data not presented).

The association between adherence with adalimumab treatment and utilization of healthcare services during the follow-up period was assessed among patients followed for at least 180 days. The median number of annual primary care visits among adherent and non-adherent patients was 17.8 vs. 15.2 and of the number of annual specialist visits was 6.7 vs. 5.0, respectively (Table 3). After adjusting for multiple covariates, non-adherent patients had 1 annual primary-care visit and 0.16 secondary-care visits less than adherent patients. Moreover, non-adherent patients had a higher odds ratio of 1.94 (95% CI: 1.15–3.28) for being hospitalized at least once per year of follow-up (Table 3).

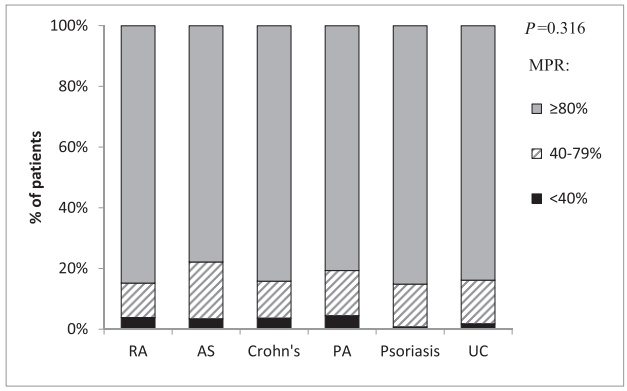

Figure 2

Medication possession ratio from first dispense to last supply day of last dispense in the study follow-up period or till discontinuation of 180 days or more according to indication ($n = 1279$*)* Four patients hospitalized >20% of the follow-up period and 56 patients with a single dispense were excluded. RA, rheumatoid arthritis; AS, ankylosing spondylitis; PA, psoriatic arthritis; UC, ulcerative colitis

Persistence with treatment

About half (52.4%) of the study patients stopped adalimumab treatment for 180 days or more; this number included discontinuations. No correlation was found between low adherence and treatment discontinuation ($r = 0.031$, $P = 0.259$). Baseline characteristics of persistent adalimumab users and of those who discontinued treatment are shown in Supplementary Table S2. Median time to discontinuation of therapy differed across medical conditions. It was shortest for RA (16 months) and longest for AS (27 months) (Figure 3). UC had shorter median drug survival than did CD (Figure 4). Among RA patients, concomitant treatment with methotrexate was associated with higher persistence rates throughout the years; however, this difference was not statistically different compared to patients who were treated with adalimumab as monotherapy (Figure 5).

Table 4 shows mutually adjusted associations between patient factors and persistence with adalimumab. Compared to low SES, high SES was associated with longer drug persistence, while concomitant steroid use was associated with earlier cessation of adalimumab. UC patients were at higher risk for drug discontinuation than patients with other indications.

Discussion

Deciphering patterns of drug behaviour is difficult given the inconsistency in definitions and the lack of a uniform

Table 2

Characteristics of adherent and non-adherent patients (n = 1279)

Characteristic	Adherent patients MPR ≥ 80% (n = 1059)% (n)	Non-adherent patients MPR < 80% (n = 220)% (n)	P-value
Age (mean, SD)	43.6 (15.3)	41.7 (13.6)	0.079
Female sex	54.8 (580)	55.0 (121)	1.0
SES score (1–20 scale; mean, SD)	11.0 (5.8)	10.2 (5.9)	0.074
Missing SES score	14.5 (154)	17.3 (38)	0.302
District			0.734
Centre	67.4 (714)	69.1 (152)	
North	19.1 (202)	16.8 (37)	
South	13.5 (143)	14.1 (31)	
Ever smoked	19.3 (204)	24.1 (53)	0.125
BMI (kg m^{-2})			0.695
<25	24.5 (259)	22.3 (49)	
26–30	28.0 (297)	26.8 (59)	
>30	24.3 (257)	24.1 (53)	
Unknown	23.2 (246)	26.8 (59)	
Disease			0.273
Rheumatoid arthritis	19.5 (43)	22.5 (238)	
Ankylosing spondylitis	20.5 (45)	14.9 (158)	
Crohn's disease	21.4 (47)	24.1 (255)	
Psoriatic arthritis	21.8 (48)	18.9 (200)	
Psoriasis	9.1 (20)	10.7 (113)	
Ulcerative Colitis	7.7 (17)	9.0 (95)	
Clinical history			
Cardiovascular disease	8.2 (87)	5.0 (11)	0.136
Diabetes	9.3 (98)	8.2 (18)	0.708
Hypertension	20.8 (220)	15.0 (33)	0.062
Chronic kidney disease	6.8 (72)	4.5 (10)	0.276
History of cancer	5.0 (53)	1.8 (4)	0.057
Utilization of healthcare services in baseline year, median (IQR)			
Primary care visits	20.0 (12.0, 31.0)	17.0 (11.0, 27.0)	0.020
Secondary care visits	8.0 (4.0, 13.0)	7.0 (3.75, 12.0)	0.046
≥1 Hospitalization	29.3 (310)	20.5 (55)	0.174
Number of inpatient days among hospitalized patients (n = 365)	5.5 (2; 11)	5 (1;9)	0.275

methodology for defining adherence. This issue has not been sufficiently explored in patients with inflammatory conditions treated with biological therapies [28]. We conducted a retrospective analysis of drug behaviour using 'real-life' electronic medical record data of patients treated with adalimumab for various inflammatory conditions. In contrast to many publications underlining the low persistence rates of drug therapy in various medical disciplines, we found extremely high and even surprising rates; reaching 80% across the different inflammatory diseases we studied [15, 16, 18].

The current study demonstrates that patients relate to treatment with adalimumab differently than they do to other medications. Tkacz *et al.* [29] retrospectively analysed adherence to adalimumab, etanercept and **golimumab** among 3892 patients with RA. Overall, patients treated with golimumab, (which is administered subcutaneously once a month), were the most adherent group compared

Table 3

Multivariate adjusted comparison of health services utilization in adherent vs. non-adherent patients (n = 1217[a])

Measure	Adherent patients MPR ≥ 80% (n = 1005) Median (IQR)	Non-adherent patients MPR < 80% (n = 212) Median (IQR)	*P*-value	Adjusted difference between non-adherent vs. adherent patients (95% CI)	*P*-value
Follow-up (years)	3.07 (1.74; 4.46)	3.42 (1.99; 5.07)	0.007		
Number of primary care physician visits per year	17.8 (11.3; 28.2)	15.2 (9.2; 25.0)	0.002	−1.0 (−0.18; −0.01)	0.028
Number of specialist visits per year among patients with at least one visit in follow-up (n = 1198)	6.7 (3.6; 11.0)	5.0 (3.0; 8.3)	<0.001	−0.16 (−0.27; −0.06)	0.030
≥1 hospitalization per year during follow-up, % (n) Odds ratio for ≥1 vs. <1	9.9% (99)	11.8% (25)	0.396	1.94 (1.15; 3.28)	0.013
Number of inpatient days per year among patients with ≥1 hospitalization in follow-up (n = 476)	2.0 (0.8; 4.9)	2.0 (1.0; 4.5)	0.846	−0.15 (−0.43; −0.14)	0.307

[a]4 patients were hospitalized >20% of the follow-up period; 56 patients with a single dispense and 62 patients with less than 180 days follow-up were excluded.

All models were adjusted for follow-up days, age, sex, disease. Additional factors were included in different models according to their contribution to the model's fit. Among these factors were socio-demographics, comorbidities, baseline medications, region of residence, smoking and BMI

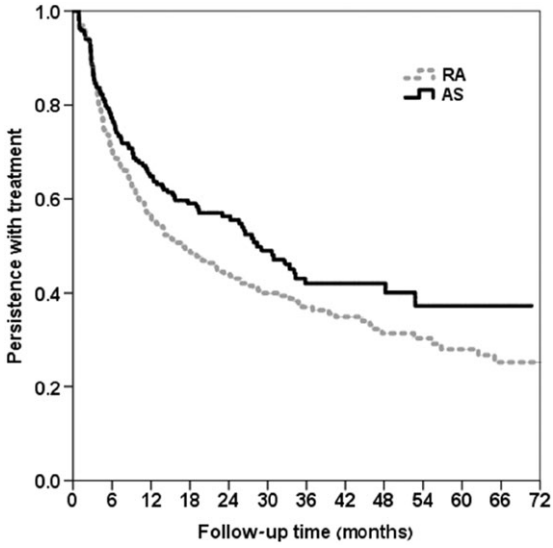

Figure 3

Kaplan–Meier plots of time to discontinuation by indication (RA vs. AS, n = 507) *P*-value from log rank test = 0.040. RA, rheumatoid arthritis; AS, ankylosing spondylitis

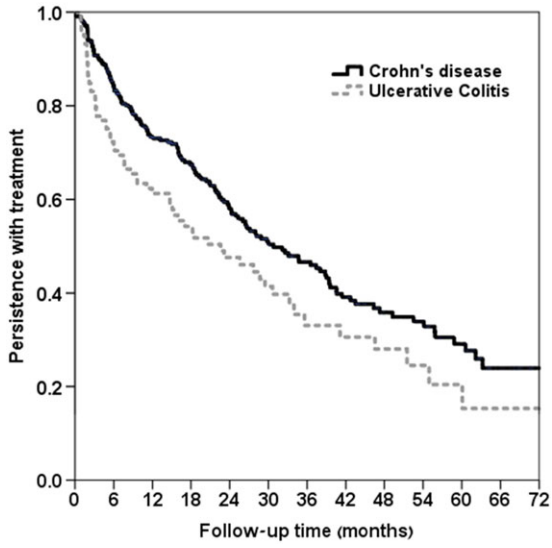

Figure 4

Kaplan–Meier plot of time to discontinuation in IBD (Crohn vs. UC, n = 433) *P*-value from log rank test = 0.011

with both adalimumab and etanercept, with MPR > 80% among 82% vs. 71% and 62%, respectively (P < 0.001). The authors speculated that better adherence to golimumab was attributable to more active disease among these patients prior to therapy and due to the more convenient dosing schedule. In contrast, Borah *et al.* [30] retrospectively analysed adherence (measured by MPR) and persistence with 1532 adalimumab, 2099 etanercept, and 261 golimumab patients with RA enrolled in a large healthcare organization. Patients were divided into current biological users and those naïve to biologic treatment (at baseline). Unadjusted adherence rates for naïve and non-naïve patients were 63% and 70% for adalimumab and 65% and 73% for etanercept, respectively.

We found that variables such as age, gender, education, smoking and socioeconomic status were not related to adherence. These associations vary between studies: while some report older patients to have better adherence, others showed that younger patients were more persistent [31].

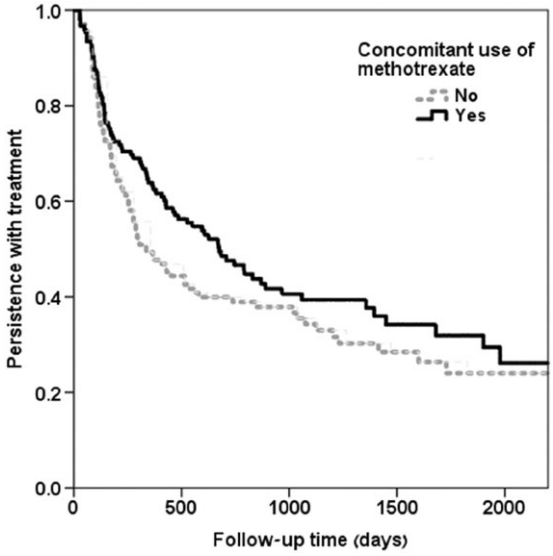

Figure 5

Kaplan–Meier plots of time to discontinuation of adalimumab in RA patients by concomitant methotrexate use; (methotrexate users n = 153, nonusers of methotrexate n = 138, total n = 291) P-value from log rank test = 0.114

Table 4

Factors associated with time to a discontinuation of ≥180 days of adalimumab treatment: multivariate Cox proportional hazards regression model[a] (n = 1335)

Variable	Hazard Ratio	95% CI	P-value
Female sex	1.14	0.98–1.33	0.089
Age (per 1 year increment)	1.01	1.00–1.01	0.010
SES tertile (1–20 scale)			
Low (1–10)	1.00 (ref.)		
Intermediate (11–14)	0.89	0.73–1.09	0.257
High (15–20)	0.74	0.60–0.91	0.002
Unknown	0.72	0.56–0.92	0.015
Immigrated after 1988	0.84	0.68–1.04	0.106
Ulcerative colitis vs. other diseases	1.32	1.02–1.71	0.034
Concomitant use of prednisone	1.46	1.22–1.75	<0.001

[a]Discontinuation was defined as ≥180-day gap in days of supply. Four patients hospitalized >20% of the follow-up period were excluded from analysis.

Since out study encompassed all ethnicities and socioeconomic strata, we believe that it provides a better understanding of drug compliance in Israel. In addition, age groups and different comorbidities that are often excluded from RCTs were also included in our study. The intermediate age group (25–34 years) was found to be less compliant, while the presence of comorbidities (additional inflammatory or cardiovascular diseases) was associated with higher adherence rates. Previous reports support the logic that the more patients are accustomed to taking medications for coexisting disorders, the higher the chances that their adherence rates will be higher and durable for additional medications [16]. This pattern was also exhibited in the current study (Table 2).

Interestingly, higher rates of adherence were associated in our study with significantly shorter hospitalizations, a finding that has pertinent medical and financial significance.

Similar to previous reports in RA patients, concomitant use of adalimumab with **methotrexate** was associated with a higher degree of adherence [32, 33]. The size of the sample was not big enough to show statistical significance, yet this trend was of no surprise given the known synergistic effects of combining methotrexate and biologicals (particularly anti-TNF agents), especially in RA [34–38].

Persistence rates to adalimumab and the continuous decline in use of the drug observed over time in our study are in accordance with those of previous reports. Koncs *et al.* [39] reviewed 13 retrospective studies regarding persistence to infliximab, etanercept and adalimumab among RA patients. Persistence decreased over time in all studies, ranging from 65% to 87% after 12 months, to 41% to 56% after 48 months. In their review, none of the medications presented superiority over the others. Data from the nationwide Danish DANBIO registry including 764 patients with PSA treated with adalimumab, **etanercept** or **infliximab**, demonstrated drug survival rates of 70% in the first year and 57% after 2 years. The crude retention rates were similar among all the anti-TNFs [40].

Several medical conditions had higher persistence rates than others, such as AS over RA (Figure 4) and CD over UC (Figure 5). This clearly shows that certain conditions are treated more effectively and result in greater improvement with adalimumab than others, as persistence serves as a surrogate marker for effectiveness. On the other hand, these observations might also reflect the limited options of alternative therapy in non-RA inflammatory conditions, since, at the time the study was conducted, the anti-**IL-17** monoclonal antibody, **secukinumab**, and the anti-**IL-12** and **IL-23** monoclonal antibody, **ustekinumab**, were not available.

Using Kaplan–Meier plots, we observed several factors influencing drug survival. We found a negative association between female sex and persistence, which might derive from women's tendency to prioritize domestic issues over health, but this is only a conjecture. Age disparities demonstrating better survival rates among the youngest age group could be because they receive support from parents that emphasizes the importance of persisting in proper drug use.

Previous studies reported prolonged drug survival in RA with concomitant MTX + anti-TNF treatment, including adalimumab [41]. It seems that this combination reduces the immunogenicity of the anti-**TNF**s in RA as well in Crohn's disease, SpA and possibly psoriasis [42].

The strength of the current study derives from the characteristics of the data which reflect actual experience, without selection bias or randomization of the recipients. Patients were included regardless of their age, sex, socioeconomic status or other comorbidities, which may confound the

outcomes of persistence and compliance. Our data therefore presents true 'drug behaviours', which by definition differs from the artificial environment of RCTs.

The main limitation of this study is that we used administrative and computerized data, which lacked more accurate clinical information regarding patient outcomes. We were unable to retrieve the reasons for drug discontinuation of each subject and whether it was related to loss of efficacy or due to safety issues. Nevertheless, it is evident that the high rates of persistence with adalimumab shown in this study clearly indicate high efficacy and a satisfactory safety profile of the medication across a wide range of clinical conditions.

Competing Interests

There are no competing interests to declare.

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Supporting Information

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http://onlinelibrary.wiley.com/doi/10.1111/bcp.13494/suppinfo

Table S1 Oral medications that were taken concomitantly to therapy with adalimumab*

Table S2 Characteristics of patients who persisted with treatment and those who discontinued treatment (n = 1335)