Clinical Rheumatology (2019) 38:2501–2508
https://doi.org/10.1007/s10067-019-04543-z

ORIGINAL ARTICLE

Outcomes of infliximab dose escalation in patients with rheumatoid arthritis

Stanley B. Cohen[1] · Joel M. Kremer[2,3] · Kimberly J. Dandreo[3] · George W. Reed[3] · Robert Magner[4] · Ying Shan[3] · Shelly Kafka[5] · Raphael J. DeHoratius[5,6] · Lorie Ellis[5] · Dennis Parenti[5]

Received: 20 January 2019 / Revised: 26 March 2019 / Accepted: 1 April 2019 / Published online: 2 May 2019
© International League of Associations for Rheumatology (ILAR) 2019

Abstract

Introduction Dose escalation of infliximab in both primary and secondary nonresponders is widely reported; however, the usefulness of dose escalation has been disputed. The objective of this analysis is to evaluate trends in clinical efficacy following multiple infliximab dose escalations in patients with rheumatoid arthritis (RA).

Methods Patients enrolled in a US RA registry were included if they initiated infliximab at 3 mg/kg every 8 weeks, received ≥ 1 infliximab dose escalation within 12 months of initiation, and had ≥ 1 visit following dose escalation. Trends in mean Clinical Disease Activity Index (CDAI) and Health Assessment Questionnaire (HAQ) scores from visits following dose escalations were evaluated.

Results In patients who received 2 or 3 dose escalations, the initial (1 or 2) dose escalations resulted in reduced mean CDAI scores, but subsequent escalations did not further reduce disease activity. In patients who received ≥ 4 dose escalations, mean CDAI scores did not further reduce disease activity over time. Mean HAQ scores were stable over time in patients who received 2 or 3 dose escalations. In patients who received ≥ 4 dose escalations, mean HAQ scores decreased following 1 dose escalation but progressively increased following subsequent dose escalations.

Conclusion Initial dose escalations (from 3 mg/kg to the equivalent of approximately 5 to 7 mg/kg) may be useful in controlling disease activity; however, there may be diminishing clinical benefit of further escalations, which can also increase the potential risk for infection and increase incremental drug costs.

Key Points

- *Initial infliximab dose escalations (1 to 2) may be useful in lowering disease activity in patients with rheumatoid arthritis.*
- *There does not appear to be a clinical benefit in infliximab dose escalations above the equivalent of 5 to 7 mg/kg.*

Keywords Dose escalation · Infliximab · Patient registry · Rheumatoid arthritis

✉ Stanley B. Cohen
arthdoc@aol.com

[1] Metroplex Clinical Research Center, 8144 Walnut Hill Lane, Suite 800, Dallas, TX 75231, USA

[2] The Center for Rheumatology, Albany Medical College, 4 Tower Place, 8th Floor, Albany, NY 12203, USA

[3] Corrona, LLC, 1440 Main Street, Suite 310, Waltham, MA 02451, USA

[4] University of Massachusetts Medical School, 55 Lake Ave North, Worcester, MA 01655, USA

[5] Janssen Scientific Affairs, LLC, 800 Ridgeview Drive, Horsham, PA 19044, USA

[6] Sidney Kimmel School of Medicine, Thomas Jefferson University, 1025 Walnut Street #100, Philadelphia, PA 19107, USA

Introduction

The goal of treatment in patients with rheumatoid arthritis (RA) is low disease activity, if not clinical remission [1, 2]. Combinations of conventional, synthetic disease-modifying antirheumatic drugs (csDMARDs) or csDMARDs plus biologic DMARDs (bDMARDs) are recommended for patients who have not achieved low disease activity or remission within 3 to 6 months of initiation of csDMARD therapy [1, 2]. Tumor necrosis factor (TNF) inhibitors have been the most commonly used bDMARDs and are usually the initial bDMARDs used for the treatment of RA [1–3].

Infliximab is a TNF inhibitor that has been approved in the United States (US) since 1999 for the treatment of moderate-to-severe RA at an initial dose of 3 mg/kg every 8 weeks [4].

In the event of an inadequate response, the prescribing information also allows for dosing up to 10 mg/kg or as often as every 4 weeks [4]. Patients with RA can fail to adequately respond to TNF inhibitors as primary nonresponders or secondary nonresponders after initial benefit [5, 6]. Observational studies have demonstrated that the mean dose of infliximab used in the clinic is approximately 5 to 5.5 mg/kg normalized to dosing every 8 weeks [7, 8].

Although dose escalation of infliximab in nonresponders is widely reported [3, 9–13], the usefulness of dose escalation has been disputed [12]. There is a lack of strong evidence that dose escalation (either by increased dose or by increased frequency of dose) improves clinical outcome in RA [5, 12–14]. The efficacy of dose escalations in real-world populations has been previously debated [3]. The efficacy of dose escalation is an important question because dose escalation may result in increased treatment cost and increase the risk of serious infection [12, 15].

To determine if infliximab dose escalation leads to progressive lowering of disease activity and an improvement in functional activity, we evaluated the trend in disease activity across infliximab dose escalations in patients with RA enrolled in the US Corrona RA registry.

Materials and methods

Patients All patients included in this study were identified from the US Corrona RA registry, an independent, prospective, observational cohort of patients with RA. Patients are recruited from 170 private and academic practice sites in the US, with 670 practicing rheumatologists. As of 02 January 2017, data have been collected on 44,532 patients with RA from 337,554 individual patient visits, representing 152,214 person-years of follow-up time. The mean duration of follow-up is 4.22 years (median, 3.46 years).

The population for this analysis included patients enrolled in the registry on or after 01 January 2007 who had a diagnosis of RA and were ≥ 18 years of age at the time of infliximab initiation. Patients had to have initiated infliximab at an initial dose of 3 mg/kg every 8 weeks and had at least 1 dose escalation in the first 12 months and at least 1 follow-up visit after the first dose escalation. Dose escalation was defined as an increase of > 1 mg/kg in dose and/or an increase in the frequency of infusion by ≥ 1 week. We standardized all doses to milligrams per kilogram every 8 weeks to make all doses and frequencies comparable. For example, a dose escalation from 3 mg/kg every 8 weeks to 3 mg/kg every 6 weeks was standardized to 4 mg/kg every 8 weeks. Follow-up included all follow-up visits in the Corrona database until the last follow-up visit recorded in the Corrona database or until it was recorded that the patient discontinued infliximab.

Data collection Data in the US Corrona RA registry, including demographics, disease status, Clinical Disease Activity Index (CDAI) and Health Assessment Questionnaire (HAQ) scores, prior medication use categories (biologics, DMARDs, prednisone), and medical comorbidity history, are collected through patient and physician questionnaires at routine clinical visits that occur every 4 to 6 months (median, 5 months). Dose is reported on the physician questionnaire as milligrams per kilogram or as the number of vials infused. If the number of vials was recorded, dose was calculated based on weight (number of vials × 100 mg/weight in kilograms). For the purposes of quantifying dose escalation, dose was rounded to the nearest integer and normalized to milligrams per kilogram every 8 weeks. Nonstandard doses (e.g., outside the 3–10-mg/kg dose range or outside a frequency of 4 to 8 weeks) were not considered (i.e., set to missing). If a dose was missing, the last dose carried forward was used.

Outcomes Outcomes included the estimated trend in mean disease activity, based on CDAI scores, and functionality, based on HAQ scores [16–18], summarized over time and scaled to the number of dose escalations (scores at visits between escalations were scaled to the proportion of time between escalations).

Statistical analyses The association of disease activity and functionality (measured by CDAI and HAQ scores, respectively) with infliximab dose escalation was evaluated using a modified time scale to align instances of dose escalation. Initiation of infliximab was considered time 0 (baseline), the first dose escalation was time 1, the second dose escalation was time 2, and so on; this convention continued similarly through all dose escalations. Visits occurring between dose escalations were measured as a proportion of time between dose escalations (or between initiation and first dose escalation). Rather than use the usual time scale for plotting mean CDAI and HAQ scores by month, a time scale that aligns instances of dose escalation was used. Mean CDAI and HAQ scores were estimated for each dose escalation time point.

The association of CDAI score with the actual infliximab dose across all visits for all patients with a dose escalation was also evaluated by plotting CDAI versus infliximab dose. The CDAI score for each patient was plotted versus the infliximab initiation dose (3 mg/kg every 8 weeks) and then versus the normalized infliximab dose at all visits following the first dose escalation. CDAI scores at visits where the patient remained at the initiation dose (3 mg/kg every 8 weeks) were not included.

Locally weighted scatterplot smoothing (Lowess curve) [19] was used to plot a graph of disease activity (measured by CDAI and HAQ) over a scaled time. This is a method of fitting a nonparametric smooth curve to the data that is empirically driven by the data. In a window around each data point,

a set of data points is used to fit a regression line to estimate the predicted value at that time point, weighing the points closest to the data point higher than those further away. This is done at every time point and results in a smooth curve that follows the data.

Cubic spline fit, an alternative plotting method [20], was used to fit splines using knots at each dose escalation. This method fits a cubic function ($ax^3 + bx^2 + cx + d$) between each dose escalation with the restriction that each curve must connect to the one preceding and the one after. This approach allows the connection of polynomial functions from knot to knot (dose escalations). Curves were estimated using Lowess and cubic spline fit for patients with any number of dose escalations and in subpopulations with 2, 3, and ≥ 4 dose escalations. Mean changes in CDAI and HAQ at each dose escalation time point were estimated from the estimated cubic spline regression model.

Results

Study population The Corrona database includes 2088 patients who initiated infliximab after 01 January 2007. Of these patients, 599 had a reported infliximab dose of 3 mg/kg at their initiation visit and 218 of these patients had at least 1 dose escalation in the first 12 months following initiation. Of the 218 who had at least 1 dose escalation, 185 had at least 1 follow-up visit after dose escalation and were included in this analysis (Fig. 1).

Demographic and clinical characteristics Patients in this analysis were mostly female (72.4%), White (82.7%), and overweight/obese (80.5%); had a mean age of 58.2 years; and had been diagnosed with RA for a mean of 7.5 years (Table 1). The mean number of prior csDMARDs taken by these patients was 1.6. Most patients were currently receiving a combination therapy (88.1%) consisting of methotrexate plus infliximab, methotrexate plus infliximab and another csDMARD, or infliximab and another csDMARD. The mean baseline CDAI score at the time of infliximab initiation was 19.6 and the mean HAQ score was 0.9.

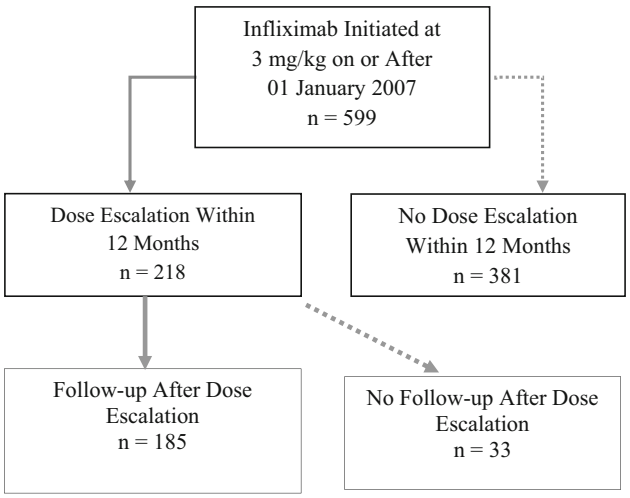


Fig. 1 Population flowchart. n, number of patients

Table 1 Demographic and clinical characteristics of patients ($N = 185$) at infliximab initiation (disease activity at visit prior to first dose escalation)

Characteristic	
Gender, female, *n* (%)	134 (72.4)
Age, years, mean (SD)	58.2 (13)
RA duration, years, mean (SD)	7.5 (8.3)
Race, White, *n* (%)	153 (82.7)
Weight, kg, mean (SD)	86.7 (21.6)
BMI category, *n* (%)	
Underweight (< 18.5 kg/m^2)	4 (2.2)
Normal weight (18.5 to < 25 kg/m^2)	32 (17.3)
Overweight (25 to < 30 kg/m^2)	53 (28.6)
Obese (≥ 30 kg/m^2)	96 (51.9)
RF+ status, *n*/*N* (%)	62/97 (63.9)
CCP+ status, *n*/*N* (%)	54/83 (65.1)
Comorbid conditions, *n* (%)	
Cardiovascular[a]	15 (8.1)
Malignancy[b]	18 (9.7)
Serious infection[c]	8 (4.8)
Diabetes	17 (9.2)
Medication history	
Prior no. of csDMARD[d], mean (SD)	1.6 (0.9)
Monotherapy, *n* (%)	22 (11.9)
Combination therapy[e], *n* (%)	163 (88.1)
MTX alone	111 (68.1)
Other csDMARD alone	21 (12.9)
MTX + other csDMARD	31 (19.0)
Prednisone use, *n* (%)	58 (31.4)
Dose ≤ 10 mg	53 (91.4)
Dose > 10 mg	5 (8.6)
Tender joint count (28), mean (SD)	5.9 (6.5)
Swollen joint count (28), mean (SD)	6.2 (6)
Physician global assessment (0–100), mean (SD)	31.3 (22.9)
Patient global assessment (0–100), mean (SD)	42.9 (27.9)
CDAI, mean (SD)	19.6 (13.2)
HAQ, mean (SD)	0.9 (0.7)
Patient-reported pain (0–100), mean (SD)	42.9 (29.3)
Patient-reported fatigue (0–100), mean (SD)	52.8 (31.4)

BMI, body mass index; *CCP*, cyclic citrullinated peptide; *CDAI*, Clinical Disease Activity Index; *csDMARD*, conventional, synthetic disease-modifying antirheumatic drug; *DMARD*, disease-modifying antirheumatic drug; *HAQ*, Health Assessment Questionnaire; *IV*, intravenous; *MTX*, methotrexate; *N*, all patients in analysis; *n*, number of patients; *no.*, number; *RA*, rheumatoid arthritis; *RF*, rheumatoid factor; *SD*, standard deviation

[a] Cardiovascular comorbidity includes myocardial infarction, stroke, acute coronary syndrome, coronary artery disease, congestive heart failure, peripheral arterial disease, and revascularization procedures

[b] Malignancy includes all cancers except for nonmelanoma skin cancer

[c] Serious infections are defined as any hospitalized infection or use of IV antibiotics

[d] Not including current DMARD

[e] In addition to infliximab

Trends in CDAI and HAQ scores The trend in CDAI scores was estimated over time scaled to instances of dose escalation using Lowess and spline curves (Fig. 2a–c). In patients who received 2 infliximab dose escalations ($n = 101$), there was a decrease in the estimated mean CDAI from the time of infliximab initiation at both the first and second dose escalation visits (Fig. 2a). In patients who received 3 dose escalations ($n = 42$), there was a progressive decrease in the estimated mean CDAI from initiation through the second dose escalation, followed by an increase in the estimated mean CDAI from the second to the third dose escalation (Fig. 2b). In patients who received 4 or more dose escalations ($n = 12$), the estimated mean CDAI remained stable over time, demonstrating little impact from dose escalations (Fig. 2c). The trend in estimated mean CDAI versus actual infliximab dose (normalized to milligrams per kilogram every 8 weeks) in all patients included in this study was similar to that observed with estimated mean CDAI versus dose escalation; there was a decrease in CDAI from 3 mg/kg every 8 weeks to 5 mg/kg every 8 weeks followed by a plateau at higher doses (Fig. 3a). The trend in the proportions of patients in remission, low disease activity, moderate disease activity, and high disease activity at each infliximab dose is shown in Fig. 3b. At 3 mg/kg every 8 weeks, no patients were in remission, approximately 50% were in high disease activity, approximately 30% were in moderate disease activity, and approximately 10% were in low disease activity. Through 10 mg/kg every 8 weeks, the proportion of patients in remission remained around 0%. At 4 mg/kg every 8 weeks, 20% to 30% of patients were in each disease-level group and remained relatively consistent for moderate and low disease activity through 10 mg/kg every 8 weeks. The proportion of patients in high disease activity was more variable, ranging between 10 and 30% through 10 mg/kg every 8 weeks.

In contrast to what was observed with the estimated trend in mean CDAI, the estimated mean HAQ scores generally remained stable in patients who received 2 (Fig. 4a) or 3 dose escalations (Fig. 4b). However, in patients who received 4 or more dose escalations, a decrease in estimated mean HAQ scores was observed from infliximab initiation through dose escalation 2, followed by a progressive increase in mean HAQ scores through subsequent dose escalations (Fig. 4c).

Fig. 2 Plot of trend of disease activity (CDAI) over scaled time. **a** The table shows the estimated mean CDAI score at each dose escalation visit and the estimated mean change in CDAI score from the start to the first dose escalation visit and from the first dose escalation visit to the second dose escalation visit. **b** The table shows the estimated mean CDAI score at each dose escalation visit and the estimated mean change in CDAI score from the start to the first dose escalation visit, from the first dose escalation visit to the second dose escalation visit, and from the second dose escalation visit to the third dose escalation visit. **c** The table shows the estimated mean CDAI score at each dose escalation visit and the estimated mean change in CDAI score from the start to the first dose escalation visit, from the first dose escalation visit to the second dose escalation visit, from the second dose escalation visit to the third dose escalation visit, and from the third dose escalation visit to the fourth dose escalation visit. Scaled time (x-axis) used initiation of infliximab as $t = 0$, time of first dose escalation as $t = 1$, time of second dose escalation as $t = 2$, and so on. Splines used knots at each dose escalation. Scatter dots are CDAI values. CDAI, Clinical Disease Activity Index; CI, confidence interval; Lowess, locally weighted scatterplot smoothing; t, time

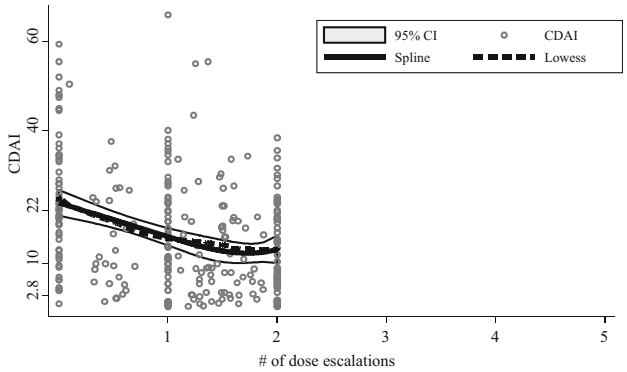
Discussion

Here, we report a retrospective, real-world, observational analysis conducted using data from patients in the US Corrona RA registry who initiated infliximab therapy at 3 mg/kg and experienced at least 1 dose escalation. In this analysis, estimates of mean CDAI scores following infliximab dose escalation indicated that, in general, in patients who received 2 dose escalations, the first 2 dose escalations (generally from 3 to 5 or 7 mg/kg or from 3 mg/kg every 8 weeks to 5 mg/kg every 8 weeks then 5 mg/kg every 6 weeks) resulted in a decrease in mean CDAI scores. However, in patients who received 3 dose escalations, following an initial decrease in mean CDAI after the first 2 dose escalations, there was a little subsequent reduction in disease activity. Further, in patients who received 4 or more dose escalations, mean CDAI scores did not decrease from initiation through 5 dose escalations. Dose escalation had little impact on mean HAQ scores. In patients who received 2 or 3 dose escalations, mean HAQ scores remained stable. In patients who received 4 or more dose escalations, mean HAQ scores decreased slightly following the first 2 dose escalations, but then progressively increased from the second through the fifth dose escalations.

The limited benefit observed with 3 or more dose escalations in this analysis in a real-world population is consistent with the results of the START randomized controlled trial [13]. In START, more than 80% of patients achieved a response with up to 3 infliximab dose escalations, but none of the 7 patients who received a fourth dose escalation due to continued disease activity responded. It should be noted that the definition of response to dose escalation in START was a ≥ 20% improvement from the baseline in the total number of tender or swollen joints only and not an American College of Rheumatology (ACR) or CDAI score. In addition, a previous small, double-blind clinical trial failed to show improved efficacy with escalation of infliximab from 3 to 5 mg/kg [12]. Together, these results suggest that although the first and second infliximab dose escalations may be effective in some patients, further dose escalations do not incrementally improve efficacy.

A post hoc analysis of data from the RISING study demonstrated that European League Against Rheumatism (EULAR) responses and decreases in disease activity (assessed using disease activity score in 28 joints [DAS28] based on C-reactive protein and the ACR core set) were significantly better with 10 mg/kg infliximab versus 3 and

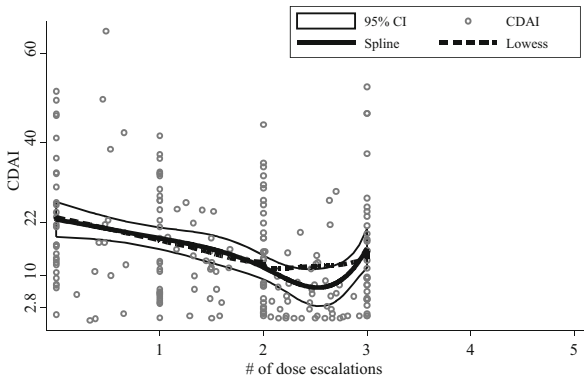
a



Mean CDAI (95% CI)	23.68 (20.81, 26.56)	16.06 (14.13, 17.99)	13.20 (10.10, 16.30)
Mean Change in CDAI (95% CI)		-7.63 (-10.81, -4.44)	-2.85 (-6.68, 0.97)

Mean CDAI scores in patients with 2 dose escalations (n = 101) showing both Lowess and spline curves decreasing from infliximab initiation visit to visit following the first dose escalation and decreasing slightly from visit following the first dose escalation to visit following the second dose escalation;

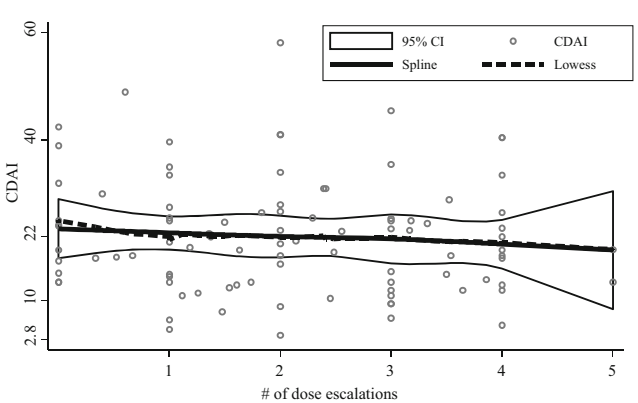
b



Mean CDAI (95% CI)	22.69 (18.79, 26.59)	18.45 (16.03, 20.87)	11.90 (9.21, 14.59)	16.19 (11.81, 20.57)
Mean Change in CDAI (95% CI)		-4.24 (-8.04, -0.44)	-6.55 (-8.87, -4.23)	4.29 (-0.96, 9.54)

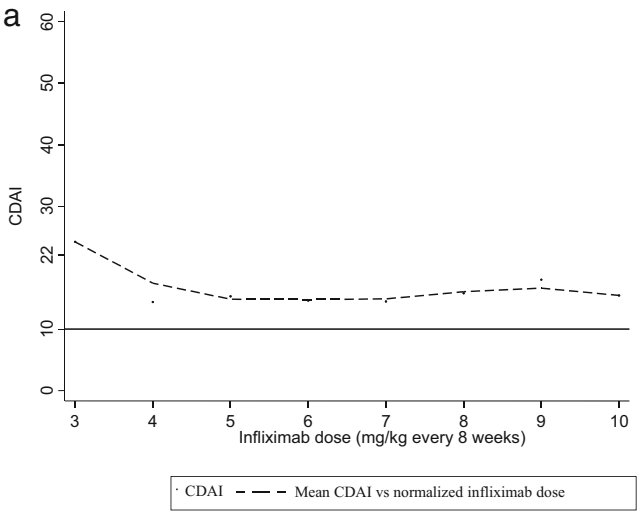
Mean CDAI scores in patients with 3 dose escalations (n = 42) showing both Lowess and spline curves decreasing from initiation visit to visit following the first dose escalation and from visit following the first dose escalation to visit following the second dose escalation, but increasing from visit following the second dose escalation to visit following the third dose escalation (spline curve dips between visits, but at visit following the third dose escalation is greater than at visit following the second dose escalation);

c

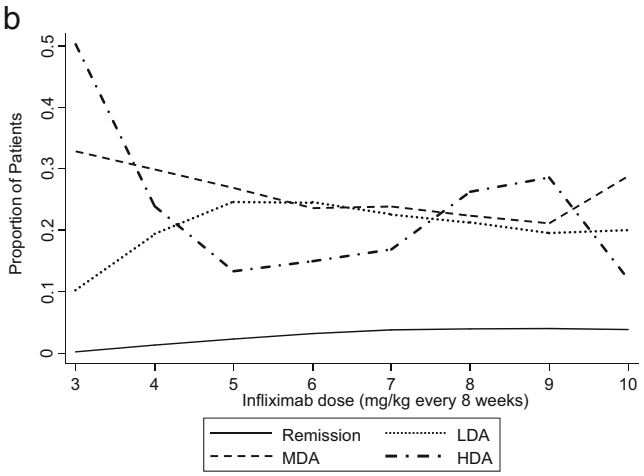


Mean CDAI (95% CI)	23.48 (17.96, 29.00)	22.73 (19.64, 25.82)	22.06 (18.15, 25.97)	21.59 (17.05, 26.13)	20.62* (16.10, 25.13)
Mean Change in CDAI (95% CI)		-0.75 (-5.49, 3.98)	-0.67 (-3.75, 2.42)	-0.47 (-6.14, 5.20)	-0.97 (-6.56, 4.62)

Mean CDAI scores in patients with 4 or more dose escalations (n = 12) showing both Lowess and spline curves remaining stable through all visits (initiation through visit following the fifth dose escalation).
*Estimated mean CDAI at fourth or fifth dose escalation visit.



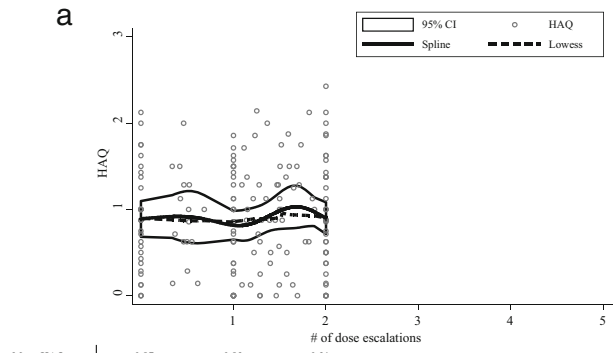
Smoothed Lowess curve of estimated predicted mean of CDAI versus actual infliximab dose showing the Lowess curve decreasing up to 5 mg/kg every 8 weeks then remaining stable through 10 mg/kg every 8 weeks. Predicted mean of CDAI was estimated using a mixed linear regression model with patients as random effect to account for multiple visits per patient. A reference line (solid line) is set at CDAI of 10, the cutoff for low disease activity (i.e., low disease activity is defined as CDAI = 10). CDAI, Clinical Disease Activity Index; Lowess, locally weighted scatterplot smoothing.



Smoothed Lowess curves of estimated proportions of patients at each disease activity level showing almost no patients in remission (solid line) from 3 to 10 mg/kg; 50% of patients in high disease activity (dotted and dashed line) at 3 mg/kg, decreasing to approximately 20% at 4 mg/kg and remaining between 10 and 30% through 10 mg/kg; approximately 30% of patients in moderate disease activity (dashed line) at 3 mg/kg and remaining between 20 and 30% through 10 mg/kg; and approximately 10% of patients in low disease activity (dotted line) at 3 mg/kg, increasing to 20% at 4 mg/kg and remaining between approximately 20 and 25% through 10 mg/kg. The proportion of patients at each disease activity level was estimated using a mixed logistic regression model with patients as random effect to account for multiple visits per patient. HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity.

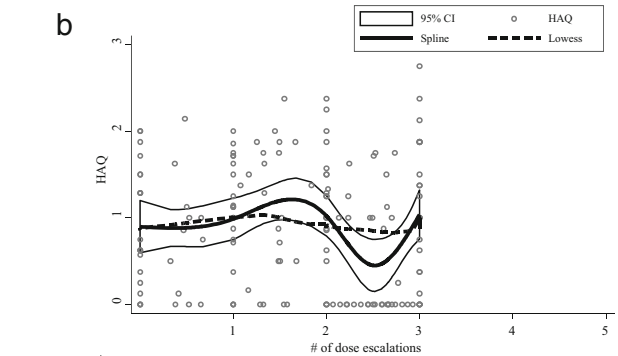
Fig. 3 Smoothed Lowess curves versus actual infliximab dose (normalized to mg/kg every 8 weeks)*. *At the initiation dose (3 mg/kg every 8 weeks) and all doses following the first dose escalation

6 mg/kg only in patients with high baseline TNF values (≥ 1.65 pg/ml) [21]. In contrast, when we looked at CDAI scores at increasing infliximab doses, we did not observe improvement at 10 mg/kg infliximab. However, because this was an observational study, the baseline TNF values of the patients in this study are not known.



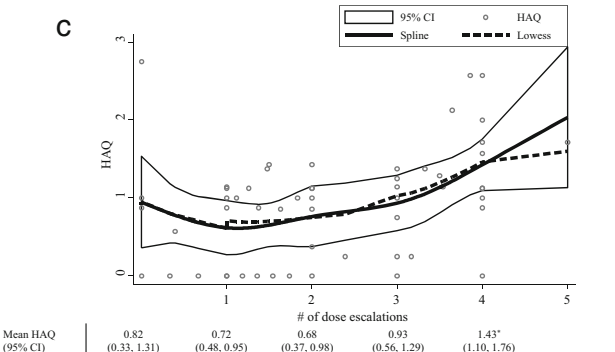
Mean HAQ (95% CI)	0.87 (0.68, 1.06)	0.89 (0.77, 1.01)	0.91 (0.73, 1.10)
Mean Change in HAQ (95% CI)		0.02 (-0.18, 0.22)	0.03 (-0.20, 0.25)

Mean HAQ scores in patients with 2 dose escalations ($n = 70$) showing both Lowess and spline curves remaining stable from infliximab initiation through visits following the first and the second dose escalations; the table shows estimated mean HAQ score at each dose escalation visit and estimated mean change in HAQ score from the start to the first dose escalation visit and from the first dose escalation visit to the second dose escalation visit.



Mean HAQ (95% CI)	0.83 (0.56, 1.10)	1.08 (0.92, 1.24)	0.96 (0.78, 1.14)	1.05 (0.77, 1.33)
Mean Change in HAQ (95% CI)		0.25 (-0.01, 0.51)	-0.12 (-0.28, 0.04)	0.09 (-0.25, 0.44)

Mean HAQ scores in patients with 3 dose escalations ($n = 30$) showing both Lowess and spline curves remaining stable from initiation through visits following the first through the third dose escalations (spline curve goes above the Lowess curve between the first and second dose escalation visits and goes below the Lowess curve between the second and third dose escalation visits, but meets the Lowess curve at each dose escalation visit); the table shows the estimated mean HAQ score at each dose escalation visit and the estimated mean change in HAQ score from the start to the first dose escalation visit, from the first dose escalation visit to the second dose escalation visit, and from the second dose escalation visit to the third dose escalation visit.



Mean HAQ (95% CI)	0.82 (0.33, 1.31)	0.72 (0.48, 0.95)	0.68 (0.37, 0.98)	0.93 (0.56, 1.29)	1.43* (1.10, 1.76)
Mean Change in HAQ (95% CI)		-0.10 (-0.51, 0.31)	-0.04 (-0.31, 0.23)	0.25 (-0.18, 0.68)	0.51 (0.06, 0.96)

Scaled time (*x*-axis) used initiation of infliximab as $t = 0$, time of first dose escalation as $t = 1$, time of second dose escalation as $t = 2$, and so on. Splines used knots at each dose escalation. Scatter dots are HAQ values. CI, confidence interval; HAQ, Health Assessment Questionnaire; Lowess, locally weighted scatterplot smoothing; t, time. Mean HAQ scores in patients with 4 or more dose escalations ($n = 10$) showing both Lowess and spline curves decreasing from initiation to visit following dose escalation 1 and then progressively increasing through visits following the second through fifth dose escalations. *Estimated mean HAQ at the fourth or fifth dose escalation visit. The table shows the estimated mean HAQ score at each dose escalation visit and the estimated mean change in HAQ score from the start to the first dose escalation visit, from the first dose escalation visit to the second dose escalation visit, from the second dose escalation visit to the third dose escalation visit, and from the third dose escalation visit to the fourth or fifth dose escalation visit

Fig. 4 Plot of trend of function (HAQ) over scaled time

Limitations of this study include the observational, retrospective design; the descriptive nature of the study and lack of comparator group; the relatively small population; and the intrinsic, potentially confounding factors present in all observational studies that can result in selection bias. Confounding by indication, in which patients with the highest disease activity were more likely to receive dose escalations, presents the largest risk of selection bias. Other potential confounders include absolute infliximab dose, length of infliximab use, and concomitant use of other drugs such as methotrexate. In addition, because this was an observational study, data on additional factors that may impact treatment response to infliximab, such as serum trough levels, the presence of anti-drug antibodies, and methotrexate polyglutamation, were not available [22]. However, in general, none of these factors are typically measured in the clinic by rheumatologists as part of the management of patients with inflammatory arthritis due to the multiple other treatment options available. Therefore, this study does reflect trends in infliximab treatment in real-world settings across the US.

This report supports the practice of infliximab dose escalation but suggests that there may be diminishing clinical benefit beyond the initial dose escalations. This may have important clinical implications, as higher doses may be associated with increased toxicity and cost [12, 15] while only maintaining disease activity levels. As multiple other options exist for the treatment of RA, consideration of switching therapy after 1 to 2 dose escalations is supported by these observations. An assessment of the risk-benefit and the cost effectiveness of multiple dose escalations should be considered in the treatment-resistant patient.

Acknowledgments Writing support was provided by Holly Capasso-Harris, PhD, of Synchrogenix, a Certara Company, Wilmington, DE. This study was sponsored by Corrona, LLC, and the analysis and medical writing support were funded by Janssen Scientific Affairs, LLC, Spring House, PA. Corrona, LLC, Waltham, MA, has been supported through contracted subscriptions in the last 2 years by AbbVie, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Crescendo, Eli Lilly and Company, Genentech, Gilead, GlaxoSmithKline, Horizon Pharma USA, Janssen, Momenta Pharmaceuticals, Novartis, Pfizer Inc., Roche, Sun-Merck, UCB, and Valeant.

Compliance with ethical standards

Informed consent All study participants provided written informed consent. Institutional Review Board (IRB) approvals for this study were obtained from a central IRB (New England IRB, Needham, Massachusetts, USA; IRB registration number 120160610) for private practice sites and local IRBs of participating academic sites.

Conflict of interest Dr. Cohen has served as an investigator and consultant for Amgen, AbbVie, Janssen, Genentech, Pfizer, Merck, Bristol-Myers Squibb, and Roche (less than $10,000 each). Dr. Kremer is employed by and has equity interest in Corrona, LLC, and has served as a consultant for AbbVie, Amgen, Bristol-Myers Squibb, Gilead, GSK, Eli Lilly and Company, Genentech, Medimmune, Sanofi, and Pfizer Inc. (less than $10,000 each) and an investigator for AbbVie, Genentech, Eli Lilly and Company, Novartis, and Pfizer Inc. (less than $10,000 each). Ms. Dandreo is employed by Corrona, LLC. Dr. Reed is employed by and has stock ownership in Corrona, LLC. Mr. Magner is employed by Corrona, LLC. Dr. Shan is employed by Corrona, LLC. Dr. Kafka is employed by and has stock ownership in Johnson and Johnson. Dr. DeHoratius was employed by (at the time the work was conducted) and has stock ownership in Johnson and Johnson. Dr. Ellis is employed by and has stock ownership in Johnson and Johnson. Dr. Parenti was employed by (at the time the work was conducted) and has stock ownership in Johnson and Johnson.

The authors have full control of all primary data. Corrona dataset is based on a large US multicenter study adhering to a number of institutional review boards, with complex logistics. Patients did not provide consent to raw data sharing during the data collection for this purpose, and the Corrona data sharing policies do not permit raw data sharing for this purpose. An aggregated limited dataset from the current analyses is available to qualified investigators with an approved protocol. Data requests may be sent to Corrona, represented by Dr. Leslie Harrold, email lharrold@corrona.org.

References

1. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, Vaysbrot E, McNaughton C, Osani M, Shmerling RH, Curtis JR, Furst DE, Parks D, Kavanaugh A, O'Dell J, King C, Leong A, Matteson EL, Schousboe JT, Drevlow B, Ginsberg S, Grober J, St.Clair EW, Tindall E, Miller AS, McAlindon T (2016) 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 68:1–26
2. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, Nam J, Ramiro S, Voshaar M, van Vollenhoven R, Aletaha D, Aringer M, Boers M, Buckley CD, Buttgereit F, Bykerk V, Cardiel M, Combe B, Cutolo M, van Eijk-Hustings Y, Emery P, Finckh A, Gabay C, Gomez-Reino J, Gossec L, Gottenberg JE, Hazes JMW, Huizinga T, Jani M, Karateev D, Kouloumas M, Kvien T, Li Z, Mariette X, McInnes I, Mysler E, Nash P, Pavelka K, Poór G, Richez C, van Riel P, Rubbert-Roth A, Saag K, da Silva J, Stamm T, Takeuchi T, Westhovens R, de Wit M, van der Heijde D (2017) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 76:960–977
3. Cannon GW, DuVall SL, Haroldsen CL et al (2014) Persistence and dose escalation of tumor necrosis factor inhibitors in US veterans with rheumatoid arthritis. J Rheumatol 41:1935–1943
4. Infliximab package insert (2013) Janssen Biotech, Inc., Horsham. In: PA
5. Plasencia C, Jurado T, Villalba A et al (2015) Effect of infliximab dose increase in rheumatoid arthritis at different trough concentrations: a cohort study in clinical practice conditions. Front Med (Lausanne) 2:71
6. Furst DE, Keystone EC, Braun J et al (2011) Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2010. Ann Rheum Dis 70(Suppl 1):i12–i36
7. Stern R, Wolfe F (2004) Infliximab dose and clinical status: results of 2 studies in 1642 patients with rheumatoid arthritis. J Rheumatol 31:1538–1545
8. Ellis L, Le C, McDermott JD, Daniel SR (2017) Real-world, multisite, observational study of infusion time and treatment satisfaction in rheumatoid arthritis patients treated with intravenous golimumab or infliximab [poster PM548]. Poster presented at: 22nd Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research; May 20–24, 2017; Boston, MA

9. Moots RJ, Mays R, Stephens J, Tarallo M (2015) Burden of dose escalation with tumour necrosis factor inhibitors in rheumatoid arthritis: a systematic review of frequency and costs. Clin Exp Rheumatol 33:737–745
10. Fisher MD, Watson C, Fox KM, Chen YW, Gandra SR (2013) Dosing patterns of three tumor necrosis factor blockers among patients with rheumatoid arthritis in a large United States managed care population. Curr Med Res Opin 29:561–568
11. Schabert VF, Bruce B, Ferrufino CF, Globe DR, Harrison DJ, Lingala B, Fries JF (2012) Disability outcomes and dose escalation with etanercept, adalimumab, and infliximab in rheumatoid arthritis patients: a US-based retrospective comparative effectiveness study. Curr Med Res Opin 28:569–580
12. Pavelka K, Jarosová K, Suchý D et al (2009) Increasing the infliximab dose in rheumatoid arthritis patients: a randomised, double blind study failed to confirm its efficacy. Ann Rheum Dis 68: 1285–1289
13. Rahman MU, Strusberg I, Geusens P, Berman A, Yocum D, Baker D, Wagner C, Han J, Westhovens R (2007) Double-blinded infliximab dose escalation in patients with rheumatoid arthritis. Ann Rheum Dis 66:1233–1238
14. Eng G, Stoltenberg MB, Szkudlarek M, Bouchelouche PN, Christensen R, Bliddal H, Marie Bartels E (2013) Efficacy of treatment intensification with adalimumab, etanercept and infliximab in rheumatoid arthritis: a systematic review of cohort studies with focus on dose. Semin Arthritis Rheum 43:144–151
15. Joyce AT, Gandra SR, Fox KM, Smith TW, Pill MW (2014) National and regional dose escalation and cost of tumor necrosis factor blocker therapy in biologic-naïve rheumatoid arthritis patients in US health plans. J Med Econ 17:1–10
16. Aletaha D, Smolen J (2005) The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 23(Suppl 39):S100–S108
17. Anderson J, Caplan L, Yazdany J, Robbins ML, Neogi T, Michaud K, Saag KG, O'dell JR, Kazi S (2012) Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res 64:640–647
18. Fries JF, Spitz P, Kraines G, Holman H (1980) Measurement of patient outcome in arthritis. Arthritis Rheum 23:137–145
19. Cleveland WS (1993) Bivariate data. In: Cleveland WS (ed) Visualizing data. Hobart Press, New Jersey, pp 90–101
20. Newson R (2000) sg151: B–splines and splines parameterized by their values at reference points on the x–axis. Stata Tech Bull 57: 20–27, Reprinted in Stata Tech Bull Reprints 10:221–230
21. Takeuchi T, Miyasaka N, Tatsuki Y, Yano T, Yoshinari T, Abe T, Koike T (2011) Baseline tumour necrosis factor alpha levels predict the necessity for dose escalation of infliximab therapy in patients with rheumatoid arthritis. Ann Rheum Dis 70:1208–1215
22. Dervieux T, Weinblatt ME, Kivitz A, Kremer JM (2013) Methotrexate polyglutamation in relation to infliximab pharmacokinetics in rheumatoid arthritis. Ann Rheum Dis 72:908–910

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.