The International RA BIODAM Cohort for Validation of Soluble Biomarkers in Rheumatoid Arthritis: Cohort Description

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Short running title: Biomarker Validation Rheumatoid Arthritis

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ABSTRACT

Background. The OMERACT Soluble Biomarker Working Group initiated an international, multicenter, prospective study, The Rheumatoid Arthritis (RA) BIODAM cohort (NCT01476956), to generate resources for the clinical validation of candidate biomarkers predictive of radiographic progression. This first report describes the cohort, clinical outcomes, and radiographic findings.

Methods. RA patients from 38 sites in 10 countries starting or changing conventional synthetic disease-modifying anti-rheumatic (csDMARDs) drugs and/or starting tumor necrosis factor inhibitor (TNFi)

were followed for 2 years. Participating physicians were required to adhere to a treat-to-target strategy. Biosamples (serum, urine) were acquired every 3 months, radiography of hands and feet every 6 months, and ultrasound of hands and feet every 3 months in a subset. Primary endpoint was radiographic progression by the Sharp van der Heijde (vdHm-SHS) score.

Results. A total of 571 patients were recruited and 439 (76.9%) completed 2-year follow-up. At baseline, the majority was female (76%), mean age 55.7 years, and mean disease duration 6.5 years. Patients had a mean of 8.4 swollen and 13.6 tender joints, DAS44 3.8, 77.7% rheumatoid factor (RF) or anti-citrullinated peptide antibody (ACPA) positive. Percentage of patients in DAS and ACR remission at 2 years was 52.2% and 27.1%, respectively. Percentage of patients with radiographic progression (>0.5) at 1- and 2-years was 38.3% and 59.8%, respectively.

Conclusions. The RA-BIODAM prospective study succeeded in generating an extensive list of clinical, imaging (2343 radiographs), and biosample (4638 sera) resources that will be made available to expedite the identification and validation of biomarkers for radiographic damage endpoints.

INTRODUCTION

At the Outcome Measures in Rheumatology (OMERACT) 8 meeting (2006) an international special interest group was assembled to develop validation criteria for a soluble biomarker to substitute for radiographic outcome measures in clinical trials of rheumatoid arthritis (RA), psoriatic arthritis, and axial spondyloarthritis[1,2]. At the OMERACT 9 meeting there was a reappraisal of the OMERACT 8 criteria and an international consensus was generated on a final set of criteria that focused on the performance characteristics of biomarker assays, the importance of addressing potential confounders, and the essential requirement for clinical validation studies[3,4]. In addition, the group formulated a levels of evidence scheme and a study design template aimed at guiding the conduct of clinical validation studies for soluble biomarkers proposed to replace the measurement of damage endpoints in RA, PsA, and AS[5]. This prioritization for clinical validation of biomarkers also reflected the international consensus that there was a major unmet need for a modifiable prognostic biomarker that could influence the routine management of these diseases. In particular, prognostic risk prediction tools for damage endpoints based on clinical and laboratory parameters currently used in practice lack sufficient predictive capacity and clinical utility, do not address the confounding effects of changes in treatment, and few have been validated in more than one cohort[6-18]. Moreover, there are no reports which have shown in long-term studies that changes in the level of these biomarkers reflect and anticipate changes in the risk for radiographic progression so that they can be considered as valid surrogates to support

their use both in clinical trials and to monitor patients in clinical practice[19-28]. A recent systematic review has highlighted the limitations of biomarker studies for prognosis in RA, especially the lack of standardization of tests for RA-related antibodies and differences in patient characteristics across studies evaluating specific biomarkers[29].

The working group generated consensus on the following 5 objectives for an RA biomarker: 1. *Change* in the biomarker should reflect/predict *change* in the radiographic damage endpoint at the group level, so that the biomarker constitutes an endpoint for clinical trials and cohort studies, and at the individual patient level, so that the biomarker constitutes an endpoint for clinical practice. 2. *Change* in the biomarker should reflect/predict *change* in the damage endpoint *independently* of known predictors. 3. *Change* in the biomarker should correlate with the interval change in damage progression *regardless of treatment approach.* 4. The biomarker should be more responsive than routinely assessed clinical and laboratory measures associated with radiographic progression. 5. The biomarker should add prognostic information regarding radiographic progression over and above the combined information obtained from all other known predictors at both the group and individual patient level.

At OMERACT 9, this group used a Delphi approach to generate an international consensus for a minimum set of criteria with respect to study design, principal outcomes, processing of biomarker samples, and documentation of potential confounders for the conduct of a prospective observational study with patients receiving therapeutic agents from different drug classes aimed at the validation of a soluble biomarker reflecting damage endpoints according to these 5 objectives[3,5]..Such studies are essential so that a sufficiently broad spectrum of patients are included to verify external validity to the patient population typically seen in clinical practice as opposed to the highly selected patients recruited to RCTs. It was therefore considered essential in the study design to include patients with a wide spectrum of disease activity receiving diverse treatments but adhering to a treat-to-target treatment strategy (T2T). This would serve not only to optimize patient outcomes but also provide an opportunity to study the relationship between change in candidate biomarker(s) related to treatment and subsequent change in the radiographic endpoint.

The international RA BIODAM study is aimed at setting a benchmark for the design, implementation, and analysis of studies aimed at the validation of prognostic parameters, including biomarkers, which are predictive of radiographic progression in RA. The data will also be used to derive risk assessment and prognostic tools for RA based on clinical and biological parameters. In this report we provide details of the study design, baseline characteristics of patients recruited to the cohort, treatment

received during the study, primary clinical outcomes, and radiographic progression over the 2 years of follow up.

METHODS

Objectives of RA BIODAM

The primary objective of RA BIODAM was to generate data and study resources that would allow the conduct of an analysis to determine the independent predictive validity of soluble biomarkers considered to be high priority candidates for predicting structural damage in RA according to the criteria and protocol developed by the working group. It was agreed that secondary objectives would establish which clinical and laboratory predictors used in routine practice individually and in combination, have the strongest and the most consistent association with *change* in radiographic damage. Tertiary objectives aimed to test the impact of treatment on biomarkers, test statistical models to determine which may be optimal for describing the independent association between the biomarker and radiographic progression, and establish sample size requirements for future studies of candidate biomarkers.

Study Design of RA BIODAM

This was a multi-center, multi-national, prospective observational study of patients with RA and fulfilling the 2010 Rheumatoid Arthritis Classification Criteria[30] recruited consecutively from rheumatologist outpatient clinics and offices in Canada (n=9), the USA (n=5), Israel (n=1), and Europe (Denmark (n=1), France (n=6), Germany (n=4), Ireland (n=1), Italy (n=6), the Netherlands (n=4), Norway (n=1) (Trial Registration**:** Assess Structural Damage in Rheumatoid Arthritis Using Biomarkers and Radiography: Clinicaltrials.gov #: NCT01476956, https://clinicaltrials.gov/ct2/show/NCT01476956, Registered June 1 2011). First patient was recruited October 30 2011 and last patient visit was May 17 2017. Principal study design features were focused on capturing change in biomarker following change/institution of csDMARD therapy (methotrexate, sulfasalazine, hydroxychloroquine, chloroquine, leflunomide) and/or following addition of TNFi therapy (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab) as patients were observed every 3 months over a 2-year time frame. Consequently, the study recruited patients who were:

(i) starting csDMARD therapy or

(ii) changing csDMARD therapy defined as an increase in dose of methotrexate by ≥5 mg weekly to a maximum dose of 25mg weekly, add-on of an alternative csDMARD, switch to an alternate csDMARD, or

(iii) starting TNFi therapy alone or in combination with csDMARD therapy.

Disease activity was monitored systematically every 3 months using the DAS44. Changes in csDMARD and/or TNFi therapy were to be implemented according to 2010 EULAR recommendations which recommend a target of remission (REM) (DAS44 <1.6) for patients receiving csDMARD therapy in the setting of early disease (<2 years disease duration) and a target of low disease activity state (LDA) (DAS44 ≤2.4) for patients receiving TNFi in the setting of established disease and prior exposure to csDMARDs[31]. Biosamples were collected every 3 months and prior to a change in csDMARD and/or TNFi therapy. Change in TNFi therapy was prespecified as an increased dose of infliximab (3 to 5mg/kg) and/or frequency (every 8 to every 6 weeks), an increased frequency of adalimumab (every other week (eow) to weekly), a switch to a different TNFi, or a switch to an agent from a different class of biologic DMARD (bDMARD: rituximab, abatacept, tocilizumab).

High dose oral glucocorticoid therapy (as in the COBRA regime[32]) could be implemented in early RA at the start of treatment with serum/urine biomarker samples being obtained prior to implementation and on a monthly basis until therapy had been stable for at least one month at ≤10mg prednisone daily. Intra-articular steroid injections could be administered as required with a biosample being obtained prior to and one month after administration if the total dose was ≥40 mg depomedrol (or equivalent).

The study fulfilled Good Clinical Practice Guidelines, complied with the Declaration of Helsinki, and received ethical approval from the local ethics committee of each of the 38 sites (cf appendix) and all patients provided written informed consent.

Inclusion and Exclusion Criteria

Consecutive patients with RA fulfilling the 2010 RA Classification Criteria were recruited[30]. Inclusion criteria included age of 18 years or older, joint symptoms for at least 3 months, DAS44 ≥2.4, about to start or change csDMARD therapy or to start TNFi therapy. If already receiving csDMARD therapy this had to be stable for 1 month prior to baseline, and if on systemic steroid (prednisone ≤ 10mg/day allowed) this had to be stable for 1 month prior to baseline. Patients were excluded if they had already received treatment with a TNFi or other bDMARD. Additional exclusion criteria are listed in supplementary materials.

Data Collection

The following assessments were conducted at screening/baseline: age, gender, marital status, education, smoking history, ethnicity, alcohol use, recreational drug use, age at disease onset, symptom duration, number of criteria met for classification of RA, current and past medical history, past RA medication history, current treatment with csDMARD and/or steroids (dose, frequency, start date), approximate duration of treatment with current and previous csDMARD and steroids, 44 swollen and 53 tender joint count, DAS44-ESR, physician global NRS (0-10), patient self-report questionnaires (Pain NRS (0-10), patient global NRS (0-10), HAQ, fatigue NRS (0-10), SF36, RA Impact of Disease Score (RAID)[33], RA Flare), Revised ACR Functional Classification of Global Functional Status in RA[34], height, weight, vital signs, ESR, CRP, RF (IgM), ACPA (assessed by anti-cyclic citrullinated peptide antibody assay), HLA-DRB1 genotype, radiographs of hands and feet, chest radiograph and tuberculosis (TB) testing for patients about to start TNFi therapy. Efficacy outcomes were also conducted at 3-monthly follow up visits and early termination visits as well as current RA treatment (dose, frequency, start/stop date, reason for discontinuation) and treatment emergent adverse events (MEDRA coding system). Gray Scale and Power Doppler Ultrasonography (US) of hands and feet was conducted on a subset of patients every 3 months using the German US 7 Score[35].

Radiographic Assessment

Radiographs of hands (postero-anterior) and feet (antero-posterior) were obtained every 6 months using a standardized methodology and submitted centrally. Radiographic joint damage was assessed centrally according to the vdHm-SHS (range of 0–448)[36] by 2 trained assessors independently who were blinded to the patient's identity, treatment and treatment center, but who were aware of the chronology of the films with the mean score of the 2 assessors being used for analyses of the primary endpoint. Progression of radiographic joint damage over 6 month, 12 month, and 2 year intervals was prespecified as a change in radiographic score greater than the smallest detectable change (SDC), as well as by a change (in the total radiographic score) > 0.5. Adjudication of discrepant radiographs by a third reader was pre-specified on the basis of one-year change score and the smallest detectable change (SDC). This was conducted if the mean one-year change score was >SDC but change score for one of the readers was <SDC. The final scores for status and change scores for discrepant cases were then derived by calculating the average of the adjudicator scores and the scores of the primary reader with the closest value for one-year change score.

Biosample Collection, Transportation, Processing, and Storage

Serum/urine biomarkers were obtained every 3 months. A biosample manual specified procedures to ensure standardized acquisition and processing of biosamples across all sites. A blood sample for serum was taken 2-4 hours after rising and processed according to the OMERACT recommendations for the minimal handling of biomarker samples[3]. RNA samples were acquired using PAXgene tubes in all patients at Canadian study sites, and at other sites prior to the first TNFi dose and one-month later. Biosamples were stored locally at -70°C without any further processing until batch-shipped at -150°C in liquid nitrogen vessels using Cryoport Inc (Irvine, California, USA), which provides sample temperature monitoring throughout the entire shipping process. The biosamples were shipped to the RA BIODAM biorepository at the CARE ARTHRITIS LTD coordinating site (Edmonton, Canada) where they were thawed, processed into 0.5ml aliquots, and stored at -70°C.

Study Endpoints

The primary endpoint of the RA BIODAM study was radiographic joint progression according to the vDHm-SHS (range of 0–448). Secondary endpoints include the vDHm-SHS erosion score (range 0-280), and the 3- and 6-month change in biomarker level from baseline following the introduction of csDMARD or TNFi therapy.

Sample Size

The sample size calculation was based on detecting a relationship between a specified biomarker and the target outcome and used the approach to sample size calculation for logistic regression of Hsieh et al[37]. A survey was conducted among the OMERACT RA BIODAM working group to obtain estimates for four parameters needed for the calculation: probability of no progression given that the biomarker is not normal, odds of no progression when the biomarker is normal to odds of no progression when the biomarker is not normal, proportion of the sample (or population) with no progression, the amount of variation of the biomarker that is explained by the other covariates in the model (vDm-SHS, DAS44, age, sex, ACPA, HLA-DRB1-SE and interactions). A logistic regression of a binary target variable on a binary biomarker variable with a sample size of 600 observations (of which 50% are expected to not progress given the biomarker is not normal) would achieve 90% power at a significance of 0.05 to detect a biomarker with an odds ratio >3 for no progression when biomarker is normal to odds of no progression when biomarker is not normal. An adjustment for the amount of variation of the biomarker that is explained by the other covariates in the logistic regression was needed for the sample size calculation; this was estimated to be an R^2 of 0.25 based on the survey results.

Statistical Analysis

We used descriptive data to report baseline cohort demographics and disease characteristics, clinical outcomes (DAS44, HAQ) and percentage achieving clinical remission (DAS44, ACR Boolean[38]) over 2 years, and cumulative probability plots for radiographic progression. Treatment categories over the course of follow up comprised the following patient groups: A. Started on csDMARD and remained on csDMARD. B. Started on csDMARD and switched to TNFi. C. On csDMARD at baseline and remained on csDMARD. D. On csDMARD at baseline and switched to TNFi. E. Started on TNFi and remained on first TNFi. F. Started on TNFi and switched to another TNFi. G. Started on TNFi and switched to non-TNFi bDMARD. We combined data from patient categories A and C into one group (csDMARD-treated only), B and D into a second group (csDMARD switched to TNFi), and E, F and G into a third group (started on TNFi and remained on bDMARD treatment). Missing data was imputed using the last observation carried forward (LOCF) for continuous outcomes and non-responder imputation for dichotomous outcomes. Statistical comparisons of treatment groups were not conducted since this was not prespecified and was not considered amongst the objectives of the study.

RESULTS

Baseline Demographics and Disease Status.

Complete baseline data was available on 571 patients who were recruited from Oct 30 2011, and last patient visit was on May 17 2017. Each center (n=38) recruited between 1 and 60 patients (median 10.5) and 439 (76.9%) had complete 2-year follow-up. Reasons for discontinuation were: subject withdrew consent (52), subject lost to follow-up (25), major protocol violation(s) with study non-compliance (14), subject non-compliant with protocol (13), serious adverse event (10), other/unspecified (10), worsening of intercurrent medical condition (5), investigator judgment (3). Baseline patient- and disease- characteristics comparing completers and non-completers are shown in Table 1. Overall, the patient population comprised a demographically typical cohort of patients with RA, the majority being female (76%) and with mean age of 55.7 years. Mean disease duration was 6.5 years and 52% had had prior exposure to a csDMARD. Patients had active disease at baseline with a mean of 8.4 swollen joints, 13.6 tender joints, DAS28 of 5.2 and DAS44 of 3.8. The majority (77.7%) were either RF or ACPA positive with a mean CRP of 14.9 mg/L at baseline. Patients with complete 2-year follow-up had fewer comorbidities, lower levels of disease activity (DAS44, SDAI, SJC, ESR) and were more likely to be treated with oral steroids at baseline.

Serum, urine, and radiographs were obtained from 4638 (90.3% complete), 4591 (89.3% complete), and 2343 (82.1% complete) visits, respectively. US scores were obtained from 1034 visits and 130

patients had at least one assessment at 11 study sites.

The percentage of patients treated with csDMARDs remained stable over time at about 90% while the number on bDMARD increased from 41% to 52% (supplementary figure). There were 142 (24.9%) patients who were naïve to csDMARD at baseline who then started on csDMARDs and 30 (5.3%) were additionally started on TNFi therapy during the follow up. Of 195 (34.2%) patients already on csDMARD therapy at baseline, 40 (7.0%) were additionally started on TNFi therapy during follow up. There were 231 (40.5%) patients that started on TNFi at baseline, 195 of which were on concomitant csDMARD therapy. Of these 36 switched to an alternate TNFi, and 26 switched to a non-TNFi bDMARD. The percentage of patients on oral steroids decreased from 45% at baseline to 26% at follow up.

DAS and HAQ scores decreased in the first 6 months of treatment although this was less evident in those patients on csDMARDs that subsequently received TNFi therapy (Figures 1 and 2). Percentage of patients achieving DAS and ACR Boolean remission gradually increased over the course of 2 years, this again being less apparent in those on csDMARDs that subsequently received TNFi therapy (Figures 3 and 4).

Radiographs from baseline and 1 year were available in 442 patients and from baseline and 2 years in 406 patients. Mean vDHm-SHS score at baseline, 1-year, and 2-years was 17.2, 18.5, and 20.0, respectively for those completing 1- and 2-year follow-up. Smallest detectable change for radiographic progression was calculated to be 2.6 vDHm-SHS units and progression >2.6 units was observed in 48 (10.9%) at 1 year and in 91 (22.4%) at 2 years. Radiographic progression of >0, >0.5, ≥3, and ≥5 vDHm-SHS units was observed in 255 (57.8%), 169 (38.2%), 48 (10.9%), 27 (6.1%), at 1 year and in 318 (78.3%), 243 (59.9%), 91 (22.4%), 41 (10.1%) at 2 years follow up, respectively (Figures 5A and B). There were few differences between the categories of treatment.

DISCUSSION

This is the first report of the data from RA BIODAM, which was an investigator-initiated 6-year international collaborative effort to compile a unique resource of clinical and imaging data with biosamples acquired according to an international consensus for the conduct of a prognostic study and standard operating procedures for the handling, transportation, and storage of biosamples. In particular, the procedures developed for RA BIODAM ensured that biosamples from 90% of patients from 10 countries were maintained at -70C from the point of blood draw and serum extraction to the point of

creating aliquots for storage in the central biorepository in Canada. Moreover, the level of patient retention, data collection, and acquisition of radiographs over 2 years was at least comparable to many clinical trials that included on-site study oversight and source data verification[39,40].

Our data demonstrates that the RA BIODAM Cohort is characteristic of RA patients starting DMARD therapy in current clinical practice with respect to both demographics and disease status and is therefore an appropriate cohort for the validation of biomarkers. Disease activity and severity was somewhat lower than observed at baseline in recent clinical trial cohorts although patient selection for RA BIODAM only required DAS>2.4 as a disease activity parameter. A majority of patients were female, symptom duration was about 6 years, disease was active with an average of 8 swollen and 13 tender joints and DAS44-ESR of almost 4, and almost 80% were serologically positive for either RF or ACPA. Just over half had already been exposed to csDMARDs and about 40% were started on TNFi agents at baseline.

A limitation of the study is that patients who withdrew had more swollen joints and higher acute phase reactants but fewer used corticosteroids. As regards bias relative to the objectives of this study, it is possible that these patients reflect a relatively refractory cohort of patients with inadequate responses to treatment and more likely to demonstrate radiographic progression. This could limit detection of an association between certain types of biomarkers reflecting inflammation and progression of radiographic damage. However, progression >0.5 was evident in 60% of patients at the 2-year follow up. Another limitation is that the loss of these patients precludes an opportunity to examine physician and patient related factors associated with failure to adhere to the treatment strategy. However, physicians had considerable discretion regarding the type of therapy that could be instituted should patients fail to achieve the DAS target. Clinical responses and radiographic progression were comparable to those observed in previously reported cohorts that employed a T2T strategy[41-47].

In conclusion, the RA-BIODAM investigators have completed a 2-year prospective study that recruited patients with characteristic demographic and disease features of RA that culminated in an extensive list of clinical, imaging, and biosample resources that will permit the clinical validation of candidate biomarkers for radiographic damage endpoints. The resources generated in RA BIODAM will be made available to the research community to help expedite the identification and validation of such biomarkers.

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Figure Legends

1. DAS44 over 2 years in the RA BIODAM cohort according to treatment category. A. Missing data imputed by last observation carried forward. B. Observed data.
2. HAQ over 2 years in the RA BIODAM cohort according to treatment category. A. Missing data imputed by last observation carried forward. B. Observed data.
3. Percentage of patients achieving DAS44 remission over 2 years in the RA BIODAM cohort according to treatment category. A. Non-responder imputation analysis. B. Observed data.
4. Percentage of patients achieving ACR Boolean remission over 2 years in the RA BIODAM cohort according to treatment category. A. Non-responder imputation analysis. B. Observed data.
5. Cumulative probability plot of radiographic progression assessed with the vdHm-SHS score according to treatment category. A. 1-year progression. B. 2-year progression.

APPENDIX

Ethics approval and consent to participate

All patients included in this study provided written informed consent. The study was approved by the following local medical ethical committees:

Investigator	Ethics Board	Approval/Reference No.
Cheryl Barnabe	University of Calgary Conjoint Health Research Ethics Board	Ethics ID: E-24487
Gilles Boire	Comité d'éthique de la recherche en santé chez l'humain du Centre hospitalier universitaire de Sherbrooke	Pour le projet # 11-069
Carol Hitchon	University of Manitoba Bannatyne Campus Health Research Ethics Board	Ref No: H2011:177
Joanne Homik	University of Alberta Health Research Ethics Board	Pro00020927
Maggie Larché	Hamilton Integrated Research Ethics Board	Project # 12-3691
Proton Rahman	Health Research Ethics Authority of Newfoundland & Labrador	Ref # 11.351
Saeed Shaikh	Institutional Review Board Services	N/A
Carter Thorne	Southlake Regional Health Centre Research Ethics Board	SRHC# 0020-1112
Mikkel Østergaard	De Videnskabsetiske Komiteer i Region Hovedstaden	H-4-2011-085
Bernard Combe (National Approval)	Comité de Protection des Personnes Sud-Méditerranée IV	National PI Réf # 11 08 03; Nº ID-RCB: 2011-A00883-38; Réf Promoteur UF 8783 (RA BIODAM); Réf. AFSSAPS: B111182-40
Alain Cantagrel	Comité de Protection des Personnes Sud-Méditerranée IV	Réf # 11 08 03; Nº ID-RCB: 2011-A00883-38; Réf Promoteur UF 8783 (RA BIODAM); Réf. AFSSAPS: B111182-40
Maxime Dougados	Comité de Protection des Personnes Sud-Méditerranée IV	Réf # 11 08 03; Nº ID-RCB: 2011-A00883-38; Réf Promoteur UF 8783 (RA BIODAM); Réf. AFSSAPS: B111182-40
René-Marc Flipo	Comité de Protection des Personnes Sud-Méditerranée IV	Réf # 11 08 03; Nº ID-RCB: 2011-A00883-38 ; Réf Promoteur UF 8783 (RA BIODAM); Réf. AFSSAPS: B111182-40

Alain Saraux	Comité de Protection des Personnes Sud-Méditerranée IV	Réf # 11 08 03; Nº ID-RCB: 2011-A00883-38; Réf Promoteur UF 8783 (RA BIODAM); Réf. AFSSAPS: B111182-40
Thierry Schaeverbeke	Comité de Protection des Personnes Sud-Méditerranée IV	Réf # 11 08 03; Nº ID-RCB: 2011-A00883-38; Réf Promoteur UF 8783 (RA BIODAM); Réf. AFSSAPS: B111182-40
Marina Backhaus/ Gerd Burmester	Ethikausschuss 1 am Campus Charité - Mitte	Application No: EA1/255/11
Thomas Neumann	Universitätsklinikum Jena Ethik-Kommission	Bearbeitungs Nr: 3466-06/12
Wolfgang Spieler	Die Ethikkomission der Ärztekammer Sachen-Anhalt	23/12
Ingo Tarner	Ethik-Kommission am Fachbereich Medizin Justus -Liebig Universität Giessen	AZ: 40/12
Oliver FitzGerald	St. Vincent's Healthcare Group Limited Ethics and Medical Research Committee	N/A
Ori Elkayam	Tel Aviv Sourasky Medical Center Institutional Review Board (Helsinki Committee)	0146-11-TLV
Gianfranco Ferraccioli	Università Cattolica Del Sacro Cuore Facoltà di Medicina E Chirurgia "Agostino Gemelli" Comitato Ethico	Prot If (A.1135)/C.E./2011; p/797/CE 2011
Maurizio Rossini	Azienda Ospedaliera Universitaria Integrata Verona Dipartimento Direzione Medica Ospedaliera e Farmacia Comitato Etico Per La Sperimentazione	Sperimentazione n. prog. CE 2156
Leonardo Punzi	Regione Veneto Azienda Ospedaliera di Padova Comitato Etico per la Sperimentzione	Prot. N. 2554P
Marcello Govoni	Comitato Etico Della Provincia Di Ferrara	Protocollo n. 118-2011
Piercarlo Sarzi-Puttini	Ospedale Luigi Sacco, Azienda Ospedaliera - Polo Universitario, Comitato Etico Locale ET/nb	Prot. N. 272/2012/20/AP
Luigi Sinigaglia	Azienda Ospedaliera, Istituto Ortopedico Gaetano Pini, Comitato Etico	4/2011
Robert Landewé	Medisch Ethische ToetsingsCommissie van Zuyderland én van Zuyd Hogeschool	Ref: MECT 11-T-98; Ref: NL38200.096.11
Renée Allaart	Leids Universitair Medisch Centrum Commissie Medische Ethiek	Ref: METC 11-T-98; Ref: NL38200.096.11; Ref: P12.049/SH/sh

Paul-Peter Tak	Medisch Ethische Commissie, Academisch Medisch Centrum Universiteit van Amsterdam	METC 12-015
Dirkjan van Schaardenburg	Leids Universitair Medisch Centrum, Commissie Medische Ethiek, Medisch Ethische Eoetsingscommissie, voor het Slotervaartziekenhuis en Reade	Ref: MECT 11-T-98; Ref: NL38200.096.11; Nummer: U/12.014/P1204
Hilde Berner Hammer	REK Regionale Komiteer for Medisinsk Og Helsefaglig Forskningsetikk	Ref: 2011/1338
Clifton Bingham	Johns Hopkins Medicine Institutional Review Boards	Study #: NA_00052505
Philip Mease	Western Institutional Review Board (WIRB)	Study Num: 1128284; WIRB Pro Num: 20111712
Joan Bathon	Columbia University Medical Center Institutional Review Board	Protocol Number: IRB-AAAI4651
Christopher Ritchlin	University of Rochester Research Subjects Review Board	RSRB: RSRB00039665
Vivian Bykerk	Institutional Review Board of the Hospital for Special Surgery	2014-228-CR2

N/A An ethics approval number is not provided by these ethics committees

Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Three different databases were developed by the coordinating project management group CARE ARTHRITIS LTD, which were linked by the patient study ID:

1. Clinical database: clinical data was recorded in the RA BIODAM eCRF, and an interactive system of study queries was used to proactively verify data entry and address missing data within prespecified time frames.

2. Biosample biorepository: aliquoted sera, urine, and RNA biosamples were barcoded and stored at -70C.

3. Imaging repository: all anonymized DICOM radiographs of hands and feet passed quality assurance procedures.

Access to all RA BIODAM data and biosamples will be made available for academic and not-for profit entities. This will require the submission of a study proposal to the scientific committee, which can be found at www.carearthritis.com.

Authors' contributions

All authors made contributions to conception and/or implementation of the study, were involved in reviewing and revising the manuscript, and gave final approval to the version to be published.

Table 1. Baseline patient- and disease- characteristics comparing completers and non-completers in the RA BIODAM Cohort.

	All (N=571)	Completers (N=439)	Non-completers (N=132)	p-value*
Age (years), mean (SD)	55.7 (12.9)	55.6 (12.3)	56.0 (14.6)	0.80
Gender (female), n (%)	434 (76.0)	337 (76.8)	97 (73.5)	0.44
Disease duration (years), mean (SD) (N=568)	6.5 (8.0)	6.5 (8.0)	6.8 (7.8)	0.70
Disease duration <2 years, n (%) (N=568)	206 (36.3)	161 (36.9)	45 (34.1)	0.55
Current smokers, N (%)	161 (28.2%)	117 (26.7%)	44 (33.3%)	0.13
Education (years), mean (SD) (N=556)	12.6 (3.8)	12.7 (3.7)	12.5 (3.9)	0.72
Number of comorbidities, mean (SD)	1.2 (1.3)	1.1 (1.2)	1.4 (1.5)	**0.01**
RF positivity, n (%) (N=544)	370 (68.0)	290 (68.7)	80 (65.6)	0.51
ACPA positivity, n (%) (N=560)	388 (69.3)	301 (69.2)	87 (69.6)	0.93
RF and ACPA positivity, n (%) (N=555)	431 (77.7)	336 (78.3)	95 (75.4)	0.49
DAS44 ESR (0-10), mean (SD) (N=569)	3.8 (1.0)	3.8 (1.0)	4.0 (1.1)	**0.03**
DAS28 ESR (0-9.3), mean (SD) (N=566)	5.2 (1.2)	5.1 (1.1)	5.3 (1.3)	0.06
HAQ, mean (SD) (N =563)	1.1 (0.7)	1.1 (0.7)	1.2 (0.7)	**0.22**
SDAI (0-86), mean (SD) (N=563)	28.5 (12.4)	27.9 (11.7)	30.5 (14.3)	**0.04**
CDAI (0-76), mean (SD) (N=568)	26.9 (11.6)	26.5 (11.1)	28.4 (13.2)	0.09
PGA (0-10), mean (SD) (N=568)	5.7 (2.3)	5.7 (2.3)	5.8 (2.3)	0.68
Swollen joint count (0-44), mean (SD) (N=569)	8.4 (6.1)	8.1 (5.7)	9.6 (7.1)	**0.02**
Tender joint count (0-53), mean (SD) (N=569)	13.6 (9.1)	13.3 (8.6)	14.5 (10.3)	0.19
ESR (mm/h), mean (SD) (N=569)	28.7 (22.2)	27.6 (20.5)	32.7 (26.9)	**0.02**
CRP (mg/L), mean (SD) (N=566)	14.9 (23.2)	13.7 (19.9)	19.0 (31.5)	**0.02**
Previous treatment with any csDMARD, n (%) (N=571)	297 (52.0)	220 (50.1)	77 (58.3)	0.10
Current treatment csDMARD/TNFi, n (%)(N=571)				
TNFi + csDMARD	195 (34.2)	150 (34.2)	45 (34.1)	
csDMARD only	337 (59.0)	263 (59.9)	74 (56.1)	0.16
TNFi only	36 (6.3)	23 (5.2)	13 (9.8)	

non-TNFi bDMARD + csDMARD	3 (0.1)	3 (0.1)	0 (0.0)	
Current treatment with oral steroids, n (%) (N=571)	255 (44.7)	208 (47.4)	47 (35.6)	**0.02**
vdHm-SHS score (0-448), mean (SD) (N=555)	18.8 (32.5)	17.6 (31.7)	23.3 (35.6)	0.12

Comparing completers and non-completers: independent samples t-test for continuous variables and Chi^2 for categorical variables; RF, rheumatoid factor; ACPA, Anti-citrullinated peptide antibody; DAS, disease activity score; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; bDMARD, biological DMARD.

Figure 1A

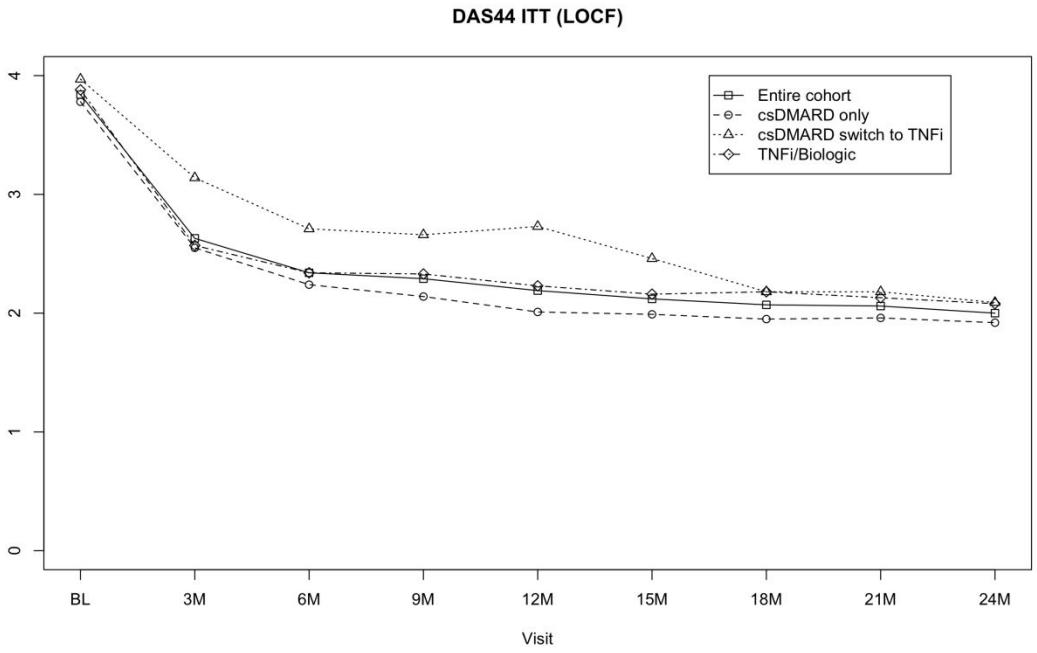
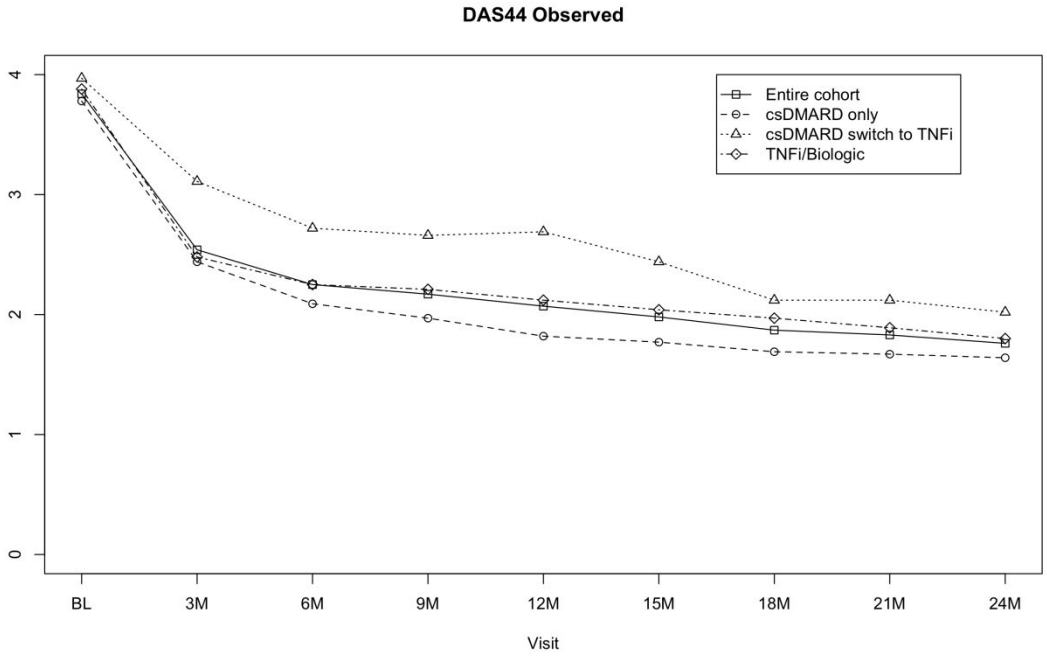


Figure 1B



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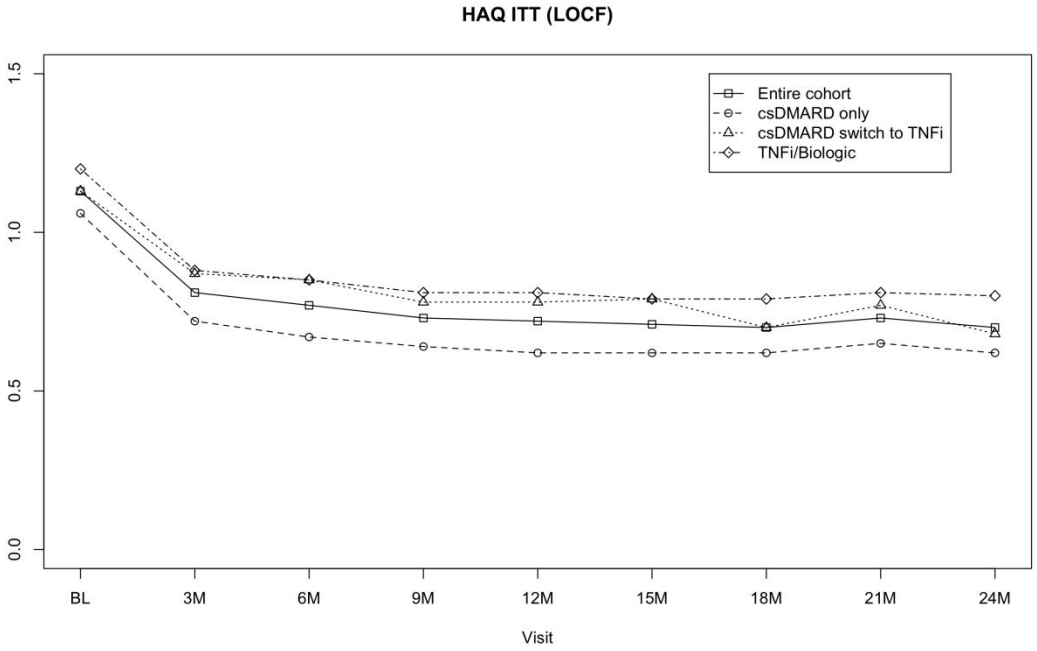

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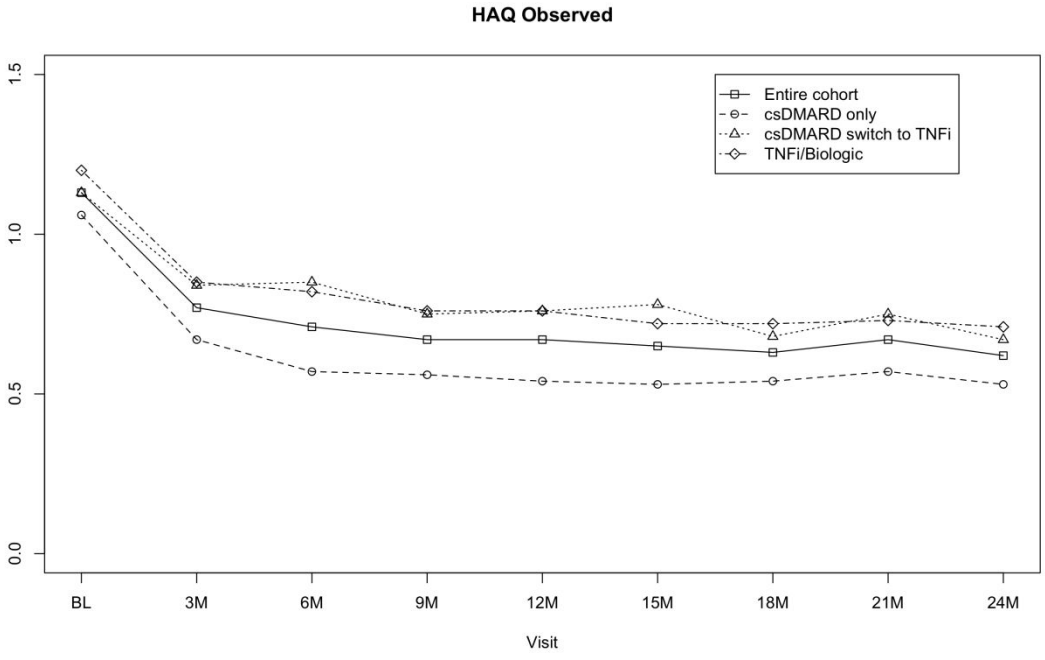

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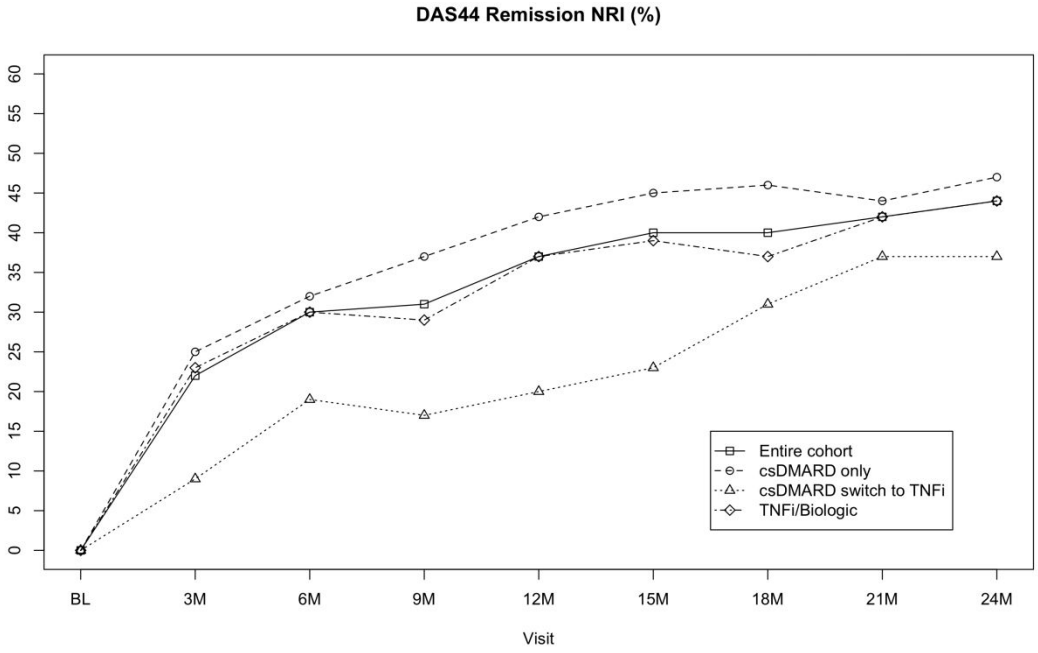

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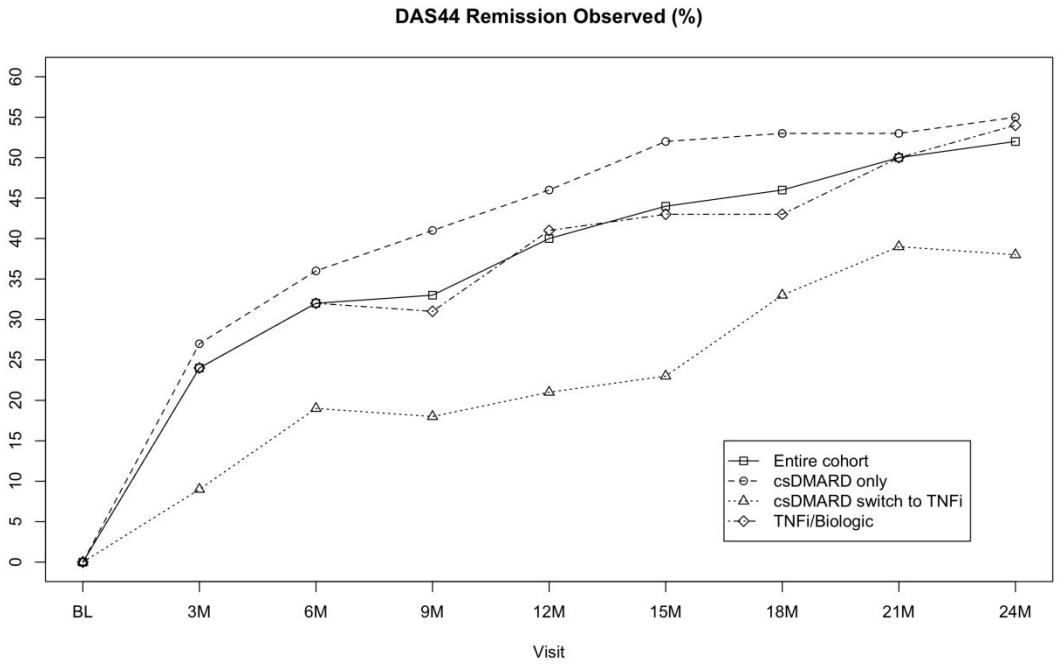

Figure 4A

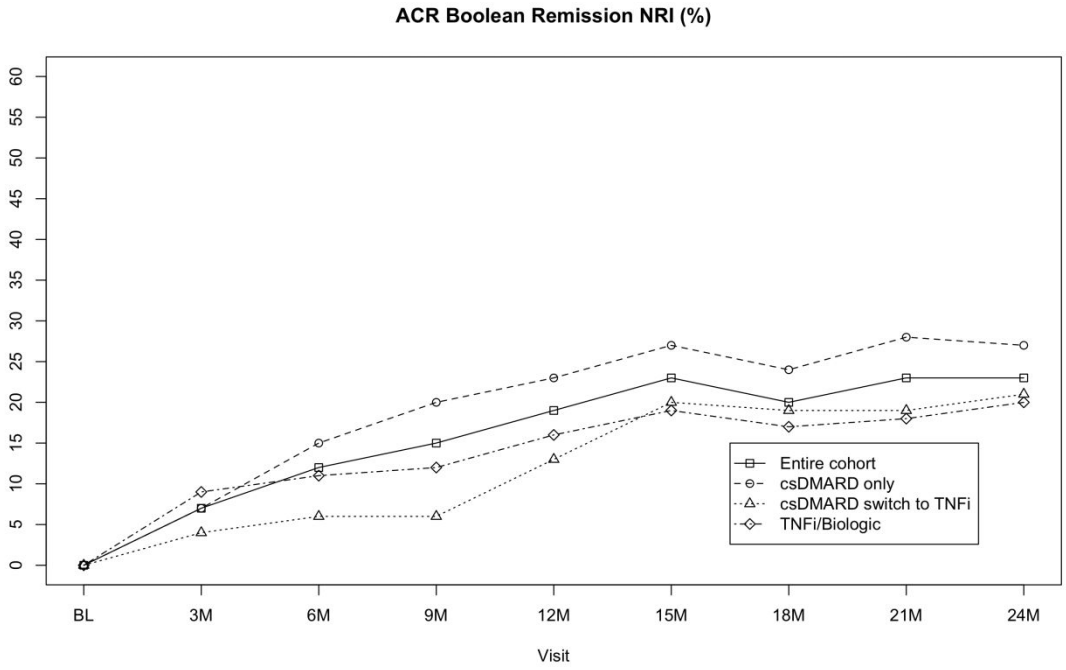

Figure 4B

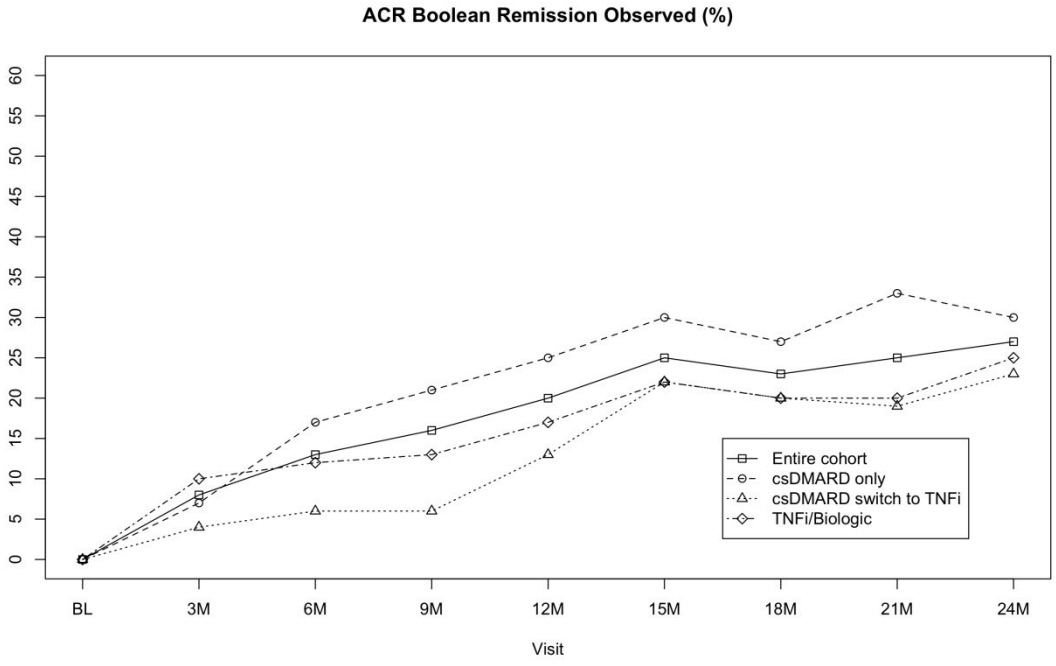

Figure 5A.

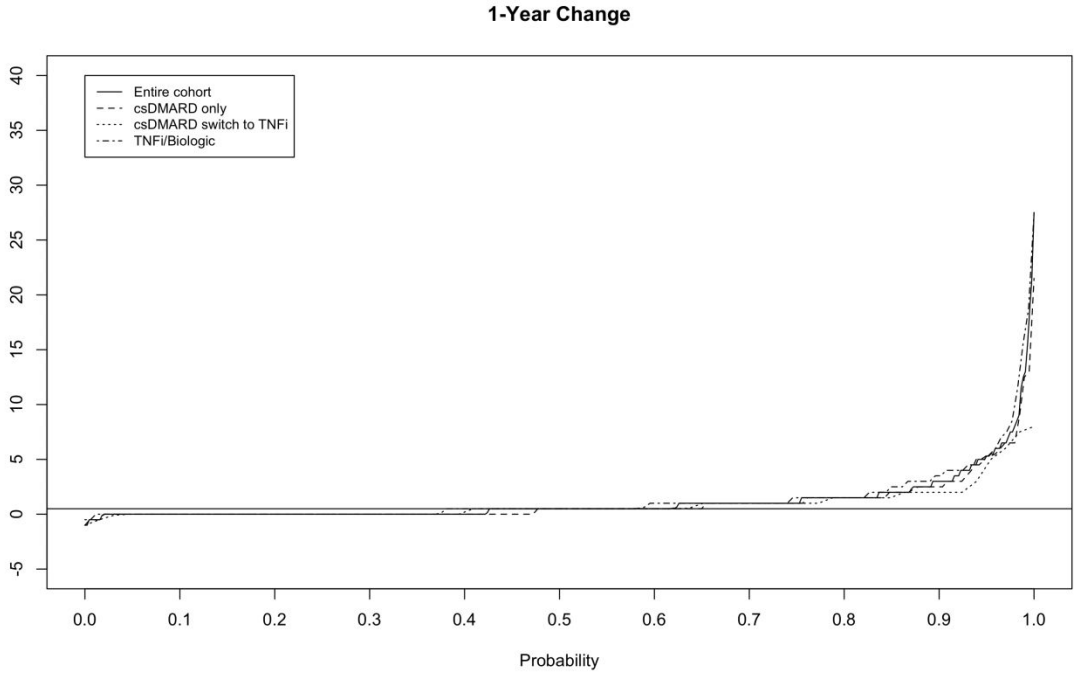

Figure 5B