RHEUMATOLOGY

Rheumatology 2011;50:40–46
doi:10.1093/rheumatology/keq263
Advance Access publication 16 September 2010

Review

Using genetic and clinical data to understand response to disease-modifying anti-rheumatic drug therapy: data from the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study

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REVIEW

Abstract

The objective of this review is to report on the progress of the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) Registry data collection and summarize previous research in understanding therapeutic response to DMARDs using clinical and genetic data. The BRASS Registry, established in 2003, is a large, single-centre, prospective and observational cohort of 1100 RA patients. Patients with either new-onset or established RA disease are recruited from the practices of rheumatologists. Annual visits collect information on demographics, 28-joint DAS-CRP3 (DAS-28-CRP3), medication use, comorbidities and functional status (Modified Health Assessment Questionnaire, Short Form Health Survey 12). Two published studies have utilized BRASS to examine genetic predictors of treatment response. In a cross-sectional study, examining the association between candidate single nucleotide polymorphisms (SNPs) and disease activity in a subset of 120 RA patients on MTX monotherapy, the minor allele of *ATIC* rs4673993 was associated with low disease activity ($P = 0.01$, DAS-28-CRP3 $\leqslant 3.2$). In an international collaboration, 55 BRASS patients receiving anti-TNF therapy were genotyped for 31 SNPs associated with the risk of RA. With our collaborators, we discovered an SNP at the protein tyrosine phosphatase, receptor type, C (*PTPRC)* gene locus that was associated with EULAR 'good response'. With accurate data collection and the capacity to run genome-wide association studies and SNP analyses, the BRASS Registry has the ability to determine the contribution of genetic variants to disease onset and to assess their usefulness as biomarkers for treatment response and drug toxicity.

Key words: Disease-modifying anti-rheumatic drugs, Anti-tumour necrosis factor, Patient registries.

Introduction

Over the last decade, TNF-α inhibitors, as well as other DMARDs, have greatly improved outcomes for RA patients. Cohort studies have demonstrated statistically significant improvements in the ACR response criteria with these therapies [1]. However, ~30% of patients do not achieve an adequate response to TNF-α inhibition as assessed by ACR response criteria [2, 3]. Questions concerning which therapies will be the most effective in treating patients with RA are not completely answered. Although several clinical variables, such as age, gender and drug inefficacy have been identified as clinical predictors of anti-TNF therapy discontinuation, we are in significant need of data to identify biomarkers of treatment response [4, 5].

National and international registries of RA patients will be instrumental in the collection of data regarding treatment efficacy. There are approximately 10 patient registries/cohort studies collecting data on rheumatic diseases and DMARD therapy, but not all of them collect additional laboratory tests beyond CRP, ESR or additional patient clinical measures like the 28-joint DAS-CRP3 (DAS-28-CRP3). The Brigham and Women's Hospital

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Submitted 1 April 2010; revised version accepted 9 July 2010.

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Rheumatoid Arthritis Sequential Study (BRASS) was developed to determine markers of treatment response and drug toxicity through the assessment of clinical variables and inherited genetic variants and patterns of gene expression. In this review, we will describe the progress of data collection for the registry and summarize previous research using BRASS clinical and genetic data to understand patient response to DMARD therapies.

History and development of the BRASS Registry

The BRASS Registry is a large, single-centre, prospective and observational cohort of 1100 RA patients. Enrolment for the registry began in March of 2003 in the Brigham and Women's Arthritis Center, which averages over 3700 RA visits per year and has minimal turnover in the patient population. The Arthritis Center provides an ideal setting for a registry due to its access to patient electronic medical records for follow-up interviews and medical record review. Funding for the registry has been from Millennium Pharmaceuticals (Cambridge, MA), Biogen Idec, Inc. (Cambridge, MA) and Crescendo Bioscience (South San Francisco, CA). Data analyses done by the study funders are shared with all registry researchers, allowing for the development of new research ideas and continued academic progress. This effort has resulted in multiple publications looking at genetic and clinical risk factors for RA susceptibility and severity [1, 4, 8–25]. BRASS is monitored by a Joint Governance Board that includes members of Brigham and Women's Hospital, all current sponsors and an internal Scientific Advisory Board.

Patient recruitment

Patients (aged $\geqslant$18 years) are recruited from the practices of attending rheumatologists and fellows at the Arthritis Center and screened for participation by International Classification of Diseases (ICD)-9 billing code diagnosis. All diagnoses of RA are then verified according to ACR criteria by the rheumatologist. Eligible patients are invited by mail to participate and are asked again by their rheumatologist during a clinic appointment. Each patient signs an informed consent form that was obtained according to the Declaration of Helsinki and approved by the Partners Institutional Review Board (IRB) at Brigham and Women's Hospital.

Data collection

At the baseline visit, physicians complete a questionnaire for each patient documenting the ACR criteria for RA diagnosis, a 28-joint count, comorbidities, infections, physician global assessment and medication information (Table 1). Since BRASS enrols RA patients with different disease duration and severity, many patients have been treated previously with DMARDs before enrolling. This requires a detailed collection of previous medication use at baseline. A trained research assistant interviews each patient and collects information on patient demographics, past and current use of all medications, smoking history and surgeries (Table 2). The patient also fills out a self-administered questionnaire that assesses functional status and quality of life. The self-administered questionnaire includes the following validated scales: Modified Health Assessment Questionnaire (MHAQ), Arthritis Self-Efficacy Scale and the Rheumatoid Arthritis Disease Activity Index (RADAI) (Table 3). Patients also have hand and wrist radiographs taken and provide blood samples for RF, CRP, anti-CCP antibodies, as well as a set of exploratory markers that include single nucleotide polymorphism (SNP) genotyping, mRNA transcriptional profiling and assessment of surface antigens by flow cytometry and peripheral serum proteins by multiplex ELISA and mass spectrometry.

Table 1 Annual physician questions

Questionnaire domains	Questionnaire time points	
	Baseline visit	Annual visit
Inclusion criteria	✓	
Health and symptoms		
Morning stiffness	✓	✓
Visual analogue scale	✓	✓
Infection/opportunistic infections	✓	✓
Extra-articular manifestations	✓	✓
Comorbidities/drug toxicities	✓	✓
28-Joint count	✓	✓
Medication changes		
Start	✓	✓
Stop/reason	✓	✓
Change/reason	✓	✓

Patient follow-up

After enrolment, annual visits are completed with each enrolled patient to collect updated information on demographics, disease activity including DAS-28-CRP3, medication use, comorbidities and functional status [MHAQ, Short Form Health Survey 12 (SF-12)]. Additional information on pregnancies, health-care resource utilization, disability, depression, quality of life and sleeping habits are collected. Blood samples, including serum, RNA and DNA, are collected annually and hand and wrist radiographs are taken every 2 years.To augment the database, patients are sent a separate self-administered questionnaire 6 months after their annual appointments. This allows for the registry to collect data regarding changes in medication use, functional status, new symptoms, conditions, antibiotic therapy and health-care resource use between the annual centre visits. In particular, the mailed questionnaire assists in recording any medication changes between annual visits and provides details on medications patients might have started and stopped during the 6 months between the annual appointment and receiving the questionnaire (i.e. antibiotics and allergy medications). Although the BRASS Registry collects detailed changes in treatment and health, it does not capture patient data at a specific time point where a

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change in therapy occurs, rather this information is collected retrospectively at the next BRASS annual visit or through the 6-month mailed questionnaires.

Status of participants

BRASS has enrolled 1105 patients since its inception and is currently in its 7th year of follow-up. Most BRASS patients have established RA when they are enrolled. Approximately 20% of patients enrolling are considered as having new onset of RA. This is defined as having symptoms for <2 years. The patient population has a mean age of 56.78 (0.44) years, with an average disease duration of 13.82 (0.39) years. The average baseline DAS-28-CRP3 score is 4.05 (0.05) and MHAQ score is 0.44 (0.47). Forty-six per cent of patients were on MTX, and 35% were on an anti-TNF agent at the time of enrolment. The baseline mean MHAQ score may seem low for a population with established disease but it is comparable with The Consortium of Rheumatology Researchers of North America (CORRONA), another RA patient registry based in the USA. In a paper assessing cardiovascular risk with RA, CORRONA researchers reported that ~80% of their patients had a disease duration >24 months and ~90% had an MHAQ score <1 ($n = 10\,156$) [26]. Additionally, the relatively low MHAQ scores indicate that this is a high-functioning group of RA patients, which may be the result of healthier patients enrolling compared with non-participants.

Currently, 772 patients are active in the study. As of January 2010, 333 patients are no longer participating in the study. Of these, 50 are deceased, 53 have moved away, 56 no longer see their rheumatologist at the

Table 2 Patient interview

Questionnaire domains	Questionnaire time points, months														
	Baseline	6	12	18	24	30	36	42	48	54	60	66	72	78	84
Demographics															
Age, years	✓		✓		✓		✓		✓		✓		✓		✓
Marital status	✓		✓		✓								✓		
Education	✓														
No. of children	✓		✓										✓		
No. of siblings	✓														
Patient birth order/birth weight			✓												
Family history (RA, comorbid)	✓	✓					✓						✓		
Ethnicity	✓														
Race	✓														
Psychosocial social support	✓		✓												
Smoking	✓		✓		✓		✓		✓		✓		✓		✓
Caffeinated beverages	✓														
Alcohol	✓		✓		✓		✓		✓		✓		✓		
General health															
Symptoms		✓	✓	✓		✓		✓		✓		✓		✓	
List of comorbidities	✓		✓		✓		✓		✓		✓		✓		✓
New conditions		✓		✓		✓		✓		✓		✓		✓	
Surgeries	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MRC Dyspnoea Questionnaire	✓		✓		✓		✓		✓		✓		✓		
Cognitive function	✓		✓		✓		✓		✓		✓		✓		
Menopause		✓					✓		✓		✓		✓		✓
Pregnancy			✓		✓		✓		✓		✓		✓		✓
Oral contraceptive use							✓								✓
Menstruation history							✓								
Use of antibiotics	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vaccinations			✓												
Daycare/teacher/health care			✓												
Teeth and gums							✓						✓		
Morning stiffness	✓		✓		✓		✓		✓		✓		✓		✓
Current and past medications															
Arthritis	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pain	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Complementary and alternative medicine			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Vitamins	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Non-arthritis medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Alternative providers	✓		✓		✓		✓		✓		✓		✓		✓
Exercise	✓		✓		✓		✓		✓		✓		✓		✓

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Table 3 Self-administered questionnaire

Questionnaire domains	Questionnaire time points, months														
	Baseline	6	12	18	24	30	36	42	48	54	60	66	72	78	84
Disease activity scales															
MHAQ	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SF-12					✓		✓		✓		✓		✓		✓
Mental Health Inventory 5	✓		✓		✓								✓		✓
Patient Health Questionnaire 9			✓								✓		✓		
EuroQol		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
RADAI	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Arthritis self-efficacy	✓		✓								✓		✓		
Flare question	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concerns about RA			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Berkman–Syme (social support)	✓		✓										✓		
Quality of Life Scale							✓								
Medical Outcomes Study Sleep Scale							✓				✓				✓
Miscellaneous															
Employment—disability and income	✓		✓		✓		✓		✓		✓		✓		✓
Health and medication insurance					✓								✓		✓
Health-care resource use		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 4 Baseline demographics

n = 1095	Mean (S.E.)
Age, years	56.78 (0.44)
Disease duration, years	13.82 (0.39)
DAS-28	4.05 (0.05)
RF titre	107.02 (7.45)
INOVA Quanta CCP titre	127.76 (4.31)
CRP titre	9.67 (0.66)
Modified RADAI	3.53 (0.07)
MHAQ score (0–3)	0.44 (0.47)
Total swollen joints (0–28)	7.80 (0.23)
Total painful joints (0–28)	8.79 (0.25)
Physician global assessment (0–10)	3.43 (0.07)
Patient global assessment (0–100)	32.83 (0.81)
Medications	*n* (%)
Pain medication	314 (30)
NSAID	506 (49)
Steroid	336 (33)
TNF inhibitor	358 (35)
MTX	471 (46)
Other DMARD	342 (33)
Female	850 (82)
New RA (within 2 years)	213 (21)

hospital, 17 are lost to follow-up, 6 had an incorrect diagnosis and 151 declined further follow-up. Baseline demographic data are shown in Table 4.

Medication data

BRASS contains 7 years of medication data collected from its participants. In 2007, Solomon *et al.* [24] assessed the validity of patient-reported medication use among BRASS participants by comparing a sample of self-reported information to the patient medical record. The agreement for current medication use was excellent, ranging from 0.71 to 0.96 depending on the medication. The agreement was lower for past medication use (0.13–0.74), suggesting that medical record review may be necessary to validate self-report of past medication use. However, having validated longitudinal medication data has given BRASS the ability to focus on treatment response to multiple drug therapies.

Biologic treatments in RA patients: clinical data

Fifty-five per cent (543) of enrolled BRASS patients have received an anti-TNF drug as treatment for their RA. Among these patients, 73% are being treated with their first anti-TNF therapy, 22% have taken two anti-TNF drugs and 5% have taken three anti-TNF drugs. Of the 543 patients who have received anti-TNF therapy while enrolled in BRASS, 62% of patients began taking etanercept first, 22% began taking infliximab and 16% began taking adalimumab. Of the 111 patients who discontinued anti-TNF therapy, 65% stopped after trying one anti-TNF drug, 30% after two anti-TNF drugs and 5% after three anti-TNF drugs.

We examined disease outcomes among four groups of TNF users in the BRASS Registry: (i) patients still using their first anti-TNF; (ii) patients using a second or third anti-TNF; (iii) patients who stopped anti-TNF therapy after trying one drug; and (iv) patients who stopped anti-TNF therapy after two or more anti-TNF drugs. The mean DAS-28-CRP3 was within the moderate level (3.2–5.1) for all groups. However, current users of a first anti-TNF had significantly lower mean DAS scores than all other groups ($P = 0.0006$). Among 94 subjects who initiated anti-TNF therapy and remained on it, mean DAS scores fell from 4.2 (95% CI 3.9, 4.6) to 2.8 (95% CI 2.5, 3.1). Mean fatigue scores were significantly higher

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for current users of a second or third anti-TNF drug compared with current users of a first anti-TNF drug ($P = 0.03$). There were no differences in MHAQ scores between groups ($P = 0.08$).

The majority of RA patients benefited from and tolerated anti-TNF therapy, with ~80% of RA patients who started anti-TNF therapy remaining with the treatment for an average of 44 months. There was no significant difference in MTX (47%) and NSAID (46%) use between groups ($P = 0.72$ and 0.88, respectively). However, the percentage of patients using steroids is 32% for ongoing first anti-TNF users, 50% for ongoing multiple anti-TNF users, 49% for patients who stopped after one anti-TNF and 67% for patients who stopped anti-TNF therapy after multiple drugs ($P < 0.0001$) [1, 25].

Disease-modifying anti-rheumatic treatments in RA: genetic data

BRASS participants are genotyped using the Affymetrix 100K and 6.0 platforms (Santa Clara, CA) allowing us to look at genetic associations to predict response to DMARDs. In a cross-sectional study of 556 RA patients in BRASS, we examined the association between candidate SNPs and disease activity in RA patients on MTX. Candidate SNPs were chosen after researching the literature for other candidate gene studies of MTX treatment response. To be included in the study, the candidate SNPs had to be associated ($P < 0.05$) with MTX treatment in one prior study of more than 100 RA patients. These SNPs, or close proxies of these SNPs, also had to be included on the Affymetrix 100K chip. The final list of included SNPs included *ATIC* rs4673993 ($r^2 = 0.96$ with *ATIC* rs2372536), *ITPA* rs1127354 and *MTHFR* rs1801133. The primary results, which looked specifically at 120 patients on MTX monotherapy, showed those carrying the minor allele of *ATIC* SNP rs4673993 were more likely to have low disease activity ($P = 0.01$, DAS-28-CRP3 $\leqslant 3.2$) after adjusting for disease duration and anti-CCP status. Results also showed that among patients on any combination of MTX, the minor allele of *ATIC* rs4673993 was associated with low disease activity, after adjusting for disease duration, anti-CCP status, anti-TNF use and gender ($P = 0.04$) [11].

Recently, 55 RA patients from BRASS on anti-TNF therapy were included in an international collaboration to test whether established RA genetic risk factors also influence response to anti-TNF therapy. With nine separate cohorts participating, 1283 RA patients receiving anti-TNF therapy were genotyped for 31 SNPs associated with the risk of RA and tested for association with treatment response. The larger sample size allowed researchers to find an SNP at the protein tyrosine phosphatase, receptor type, C (*PTPRC,* also known as the *CD45*) gene locus that was associated with the primary endpoint, EULAR 'good response' *vs* 'no response' [rs10919563, odds ratio (OR) = 0.55, $P = 0.0001$] after adjusting for age, gender and MTX use. Researchers also found suggestive evidence of a stronger association in RF/CCP autoantibody-positive (OR = 0.55, 95% CI 0.39, 0.76) compared with autoantibody-negative patients (OR = 0.90, 95% CI 0.41, 1.99), which was also adjusted for age, gender and MTX use [4].

Challenges of clinical and genetic research in patient registries

Because BRASS is not a clinical trial it faces the same issues as all observational registries. Statistically, clinical trials are considered more reliable because participants are randomly assigned to treatment groups, which minimizes bias and confounding. However, observational registries allow researchers to study multiple variables and the effect of each variable on the probability of developing the outcome of interest. Also, observational registries are considered more representative of the real-world population and provide data on real-world treatment choices, because they typically involve hundreds to thousands of patients and usually have less-stringent inclusion criteria than clinical trials. Therefore, observational registries, like BRASS, may provide data that are more representative of RA treatment and disease progression [27].

Assessing treatment response in an observational cohort, like BRASS, comes with a unique set of challenges. Each registry patient enters the study with different disease durations, medication treatments and on different medication doses. Although the registry collects medication use in great detail, it can be cumbersome to understand how to best use this data. Researchers must utilize appropriate statistical methods to account for differences in duration and dosage of treatment. In addition, researchers should consider the possibility of effect modification by disease duration because associations between treatment and response may differ among patients with early disease compared with those with established disease. Confounding by indication may also occur if registry patients who have higher disease activity are more likely to be taking an anti-TNF treatment and MTX, whereas those with lower disease activity are more likely to be prescribed HCQ [28].

BRASS has provided valuable information concerning the genetic contribution of treatment response to DMARD therapy. However, even with a large registry, sample size may be too small to have the power to detect common alleles of modest effect size [12]. Thus far, at least 29 known associations have been identified between SNPs and RA risk [29], and only one of these associations has had an OR >1.4 [30]. Similarly, the ORs for associations between SNPs and treatment response are likely to be modest. In order to detect these associations, collaborations between multiple RA cohorts are necessary.

Although rewarding, collaborative studies also bring a unique set of challenges. Researchers may struggle with methods to combine data from different cohorts as many of the established cohorts differ in terms of population characteristics (e.g. early-onset disease *vs* established disease; seropositive patients *vs* seronegative patients), data collection time points, laboratory assessments (e.g. different assays) and clinical outcomes (e.g. DAS-28-CRP

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vs DAS-28-ESR). In the future, as new registries are developed and established registries mature and evolve, it will be beneficial to establish common disease measures across studies, while maintaining the unique nature of each cohort. Establishing early partnerships between new and current patient registries would be beneficial in creating long-term collaborations to further genetic and clinical RA research.

The future of the BRASS Registry

As a prospective cohort of approximately 1100 RA subjects with up to 7 years of data, BRASS is a unique resource, providing a comprehensive set of clinical and serological disease activity measures. The registry's focus has been on translational research and mainly encompasses treatment response and toxicities, though it also provides a wealth of information for investigators with other interests, including cost-effectiveness and patient-reported outcomes.

We expect that the BRASS cohort will continue to be an important resource in the discovery of new biomarkers for treatment response. As we look towards the future of RA research, we hope to expand the BRASS Registry to capture valuable information on early-onset RA and treatment-naïve patients, as well as examine the cost-effectiveness of DMARD therapies, the psychological and social effects of RA and quality of life. With accurate data collection, reliable follow-up and the capacity to run genome-wide association studies as well as SNP analyses, BRASS provides opportunities to determine the contribution of genetic variants to disease onset and severity and to assess their usefulness as biomarkers for treatment response and drug toxicity.

Rheumatology key messages

- The BRASS Registry was developed to determine biomarkers of disease response using clinical and genetic variables.
- BRASS is a unique resource, providing a comprehensive set of clinical and serological disease activity measures.

Acknowledgements

We would like to thank Nancy Maher, Anne Fossel, Mary Beth Sullivan, Gillian Quinn, Meghan Courtney, Kaitlin Fairweather and our study participants.

Funding: The BRASS is funded by Biogen Idec, Inc., Cambridge, MA, and Crescendo Bioscience, South San Francisco, CA.

Disclosure statement: D.H.S. has received research grants from Amgen and Abbott and has received educational course support from Bristol Myers Squibb. Y.C.L. holds stocks in Merck and Company, Novartis and Elan Corporation. These organizations do not stand to gain/lose financially from the publication of this article. M.E.W. has received grant support from and is a consultant for Biogen Idec and Crescendo Bioscience. N.A.S. has received research grant support from Biogen Idec, Crescendo Biosciences and Amgen. R.M.P. has received consulting fees from Merck and Biogen Idec. All other authors have declared no conflicts of interest.

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