
The Corrona US registry of rheumatic and autoimmune diseases

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ABSTRACT

The Corrona US national registry collects data concerning patient status from both the rheumatologist and patient at routine clinical encounters.

Corrona has functioning disease registries in rheumatoid arthritis, psoriatic arthritis, spondyloarthropathies, psoriasis and inflammatory bowel disease. Corrona merges data concerning long-term effectiveness and safety, as well as comparative and cost effectiveness of agents to treat these autoimmune diseases.

Historical perspective

With the proliferation of new agents for the treatment of rheumatic diseases, it was apparent early on that a system to gather so-called “real world” data would be needed in order to derive observations which could help to illuminate how safety, effectiveness, and prescribing patterns would play out in society after approval. For many years there were few treatment options available other than methotrexate (MTX), and older disease-modifying anti-rheumatic drugs (DMARDs) such as hydroxychloroquine, sulfasalazine and azathioprine. Corticosteroids were, and are still, used as ‘bridge therapy’, even though patients could remain on them for decades. But many new drugs were on the horizon.

Why registries? Are they the best source of “real world” data?

With the approval of etanercept in late 1998, it started to become evident that it would be increasingly important to harvest some data on real world performance of this drug and others which were soon to come. After all, a randomised controlled trial (RCT) is somewhat limited. The RCT is designed for regulatory approval and by its very nature must have a limited duration of exposure. The interventions in a RCT are

compared with a placebo arm in order to derive unbiased outcome measures. It is of course unethical to keep patients with active disease on placebo for prolonged periods, so the duration of exposure for derivation of odds ratios (ORs) for side effects *versus* placebo must be relatively short. There are also many inclusions and exclusions which may be necessary in RCTs (comorbidities, minimal disease and elevated acute phase response measures) which also render these trials poorly suited for the evaluation of long-term real-world outcomes. Once published, meta-analyses of RCTs can combine results of many published trials in order to derive a great deal more statistical power to determine efficacy *versus* a placebo. However, while metaanalytic techniques can add an element of understanding to the efficacy of agents, they are still limited by the same characteristics which afflict RCTs; they are comparing trials of agents studied in populations with limited exposure, fewer comorbidities, and inclusion and exclusion criteria not considered to be exclusionary in general practice. In addition, as already noted, they are poor vehicles for deriving statistical ORs for untoward events as the comparisons for these events are inevitably made with placebo interventions of very limited duration. Thus, sparse events in a placebo arm (even varying from 0–3 or 4 serious toxicities) will greatly influence the OR used to understand the risk of the event under consideration in the active intervention (1).

Given the challenges of applying studies designed for regulatory purposes necessary for drug approval (RCTs), how do practitioners, patients, payers and society determine the true value of these interventions in the real world? The answer has become observational registries. These registries now exist throughout the Western world including Western Europe, Canada and the

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J. Kremer is the chief medical officer of Corrona. He is a shareholder and has equity interest in the company.

United States (2). Together, they have become valued sources of rich epidemiologic data on the real world performance of newly approved agents. Peer-reviewed publications from these registries now number in the hundreds and are certainly far too voluminous to reference in this review.

Could registries show different results and still be valid?

It is important to consider that a registry must naturally reflect the patterns of drug utilisation in the society in which it is based. It is thus ideally representative of drug utilisation patterns within a given country or geographic area. Of note in this context, is that different European registries are primarily derived from one party socialised medicine government payment systems. This means that the government can set the rules on when and for whom the drugs can be used.

In the United Kingdom, a patient with rheumatoid arthritis must have a Disease Activity Score (DAS) DAS-28 score of 5.1 in order to be considered for a biologic agent. Similar disease activity metrics are used in other European registries with a government payment system which can set the rules on who will receive these expensive agents paid for with taxpayer money.

It would thus follow that the penetration of biologic agents is quite different in these societies with government payment compared with the United States. While the Medicare system is the largest single payer in the US (Medicare covers retired individuals over 65 years old, or on disability), it is forbidden by law for bargaining with the pharmaceutical industry to set the price of drugs. Because of the absence of any central government payment system in the US, there are many payers who will generally make available a biologic agent if it is approved by the Food and Drug Administration (FDA) for a particular disease indication. (However, these drugs are "tiered". Meaning that there are preferred drugs within a given category for which the payer has reached a particularly favourable agreement with the manufacturer. A further exploration of this topic is beyond the scope of this review.) At present, the proliferation of

biologic agents and small molecules such as Janus Kinase (JAK) inhibitors include 10 different agents, and counting. Because a single agent in a class of agents (one of the 5 TNF inhibitors) has to be on every payer's formulary, and because there are no minimal criteria for disease activity in order to receive these agents, the penetration of biologic agents for RA in the US approaches 50% and may even be higher for diseases like psoriatic arthritis.

The net outcome of these societal differences is that the data collected from Western European registries which have minimal disease criteria for eligibility results in a penetration of biologic agents which is far lower than in the US. This is indeed the case for all of the European registries. Thus, the data from these registries reflects the society from which they are derived and are not entirely comparable to a US market. If a European registry collects data on patients who entered because they have been mandated to exhibit high disease and reports that a certain outcome is observed, it is unclear if the same observation will be the case in a US registry which enters a different mix of patients which reflect the different rules for drug access in the US. Thus, US patients receiving these expensive drugs tend to have less severe disease than in Western Europe. It is generally widely accepted that certain comorbidities and toxicities are related to disease activity. Thus the differences in registries are potentially meaningful.

To expand and reiterate on this theme, if the prevalence of comorbidities and toxicities, and indeed the response to treatment, is expected to be different in individuals with different levels of disease activity, then it would follow that the observations from the registries will be expected to be different reflecting the distribution of the interventions and the patients treated in the society from which the data are derived (3).

The Corrona registry

The Corrona registry is the only US national registry which collects data at the point of encounter between a physician and a patient at the time of a routine clinic visit. Both rheumatologist and

patient complete data on disease activity which reflects the patients' status at the point of the clinical encounter. Clinically relevant information which has evolved in the period between appointments is harvested at these visits. All of the elements of Good Clinical Practice (GCP) are utilised including uniform data fields collected electronically at regular intervals. The data collected include virtually all of the elements which are typical of an RCT including joint counts, visual analogue scales for physicians and patients, laboratory values, including acute phase responses data, and diagnostic tests including rheumatoid factor and anti-citrullinated protein antibody status. In addition, radiographic outcomes are recorded in categories ranging from normal, to joint space narrowing and erosions. Classical patient-reported outcomes (PROs) are collected including a modified Health Assessment Questionnaire (mHAQ) and an EQ5d. Patient habits including smoking, alcohol consumption, and demographics including employment, disability, insurance type and status, marital status and time lost from work are routinely recorded. If medications are started or switched, the reason(s) for the start, or switch, are recorded by the treating physician. A summary of the data collected in the Corrona RA database is seen in Table IA (clinical) and Table IB (toxicities and new medical problems).

Since its founding in 2001, Corrona has enrolled over 42,000 patients with RA from 650 different rheumatologists in 40 states in the US. We have data on approximately 325,000 individual visits in the database.

Physicians are paid a fair stipend for each and every accepted visit. If pre-defined critical fields are not collected, then the site is not paid. In this way, Corrona has both a carrot and a stick to assure that critical data fields are present in the data. The data are scrutinised by Corrona for quality and completeness. Adverse events are followed up with requests for deidentified hospital records in order to confirm, validate and adjudicate these reports from the physician-patient encounter.

Because of the nature of the Corrona

Table IA. Clinical data elements in the Corrona rheumatoid arthritis registry.

28 jt count	Physician VAS*	Patient VAS*	ACR class	Radiographic description	Routine Labs	Patient-reported outcomes
CDAI/ACR 20/50/70; DAS 28	Global disease	Global disease	I-IV	Normal, joint space narrowing, erosions	CBC, CMP**, ESR, CRP, RF, anti-CCP At site	mHAQ, EQ5D; Patient demographics, smoking, alcohol, narcotics, smoking routine

Data are collected every 6 months at the time of a routine clinical encounter. Interim data are collected on the form.

*VAS: Visual analogue scale for global arthritis activity; **CMP: Complete metabolic panel including electrolytes, transaminase values, serum albumin and serum creatinine. These values are collected locally at each site.

Table IB. Side effects and new medical problems collected in the Corrona rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, psoriasis and inflammatory bowel disease registries*.

MACE events	Cancer	Infectious diseases**	Hepatic events	GI events***	Autoimmune events#	Neurological events##	Miscellaneous events
Yes (Y)	Y	Y	Y	Y	Y	Y	Y

*All events reported are confirmed by Corrona with the site which completes a 3-5 page separate report. The events are then confirmed, and validated as real by an independent committee and the adjudicated by a team of physicians as definite, probable, possible and unlikely. All MACE events are adjudicated by a team of academic cardiologists. Ascription of causality of the event is assigned by the treating physician.

**All infectious events including opportunistic infections are collected using the same system described above.

***Includes Gastrointestinal bleeds, perforations, colitis and abdominal pain.

#Includes new psoriasis, colitis, vasculitis, rash. ##Includes Multiple sclerosis and demyelinating disease. Includes confirmation evidence from MRI imaging when appropriate.

data and the depth and breadth of the data collection, we have been able to derive some unique insights on the real world performance of biologic agents, small molecules and conventional DMARDs resulting in publication of over 60 peer-reviewed manuscripts and hundreds of abstracts at national meetings.

Corrona: what's next?!

We believe that a real world US-based, robust observational registry will become even more important in the coming years with the proliferation and dissemination of biosimilar agents. Patients, practitioners, payers, CMS, and society in general deserve to see real world US-derived data on the performance of these agents compared with originator drugs. How will Comparative (CER) and Cost Effectiveness (CE) compare across biosimilars and their originator? How will they compare across, and within, biosimilars as a separate class?

Biosimilars are attractive to payers and patients as they should be less expensive. But relative expense begs the question of Cost Effectiveness (CE)? Will these agents prove to be more CE,

Table II. Corrona registries for autoimmune diseases*.

RA, 2001-present	Psoriatic arthritis, 2015-present	Spondyloarthritis, 2015-present	Psoriasis, 2015-present	IBD** 2016	Multiple sclerosis 2017 (projected)
Active and growing	Active and growing	Active and growing	Active and growing	FPI 2016	FPI 2017

*All Targeted Adverse Events are collected using the same designations and categories across all of the registries to facilitate comparisons. All events in all registries are confirmed, validated and adjudicated as described. All specific data elements are designed by academic leads to reflect the key core elements of data within each disease that are captured in randomised controlled trials. See text for in depth description of RA registry.

**IBD: Inflammatory Bowel Disease and includes both Crohn's Disease and Ulcerative Colitis.

Table III. Sources of data for Corrona disease registries.

Clinical visit, physician and patient	Patient App from mobile devices and home computer	Claims data
Ongoing	Q1 2017	Q1 2017

or will patients and prescribers have to sacrifice either effectiveness or safety? In addition, biosimilars will be used for disease indications for which the originator drug is approved, but may never have been studied in the development process. This is called extrapolation of indications. Who should monitor the performance of these agents when extrapolated to indications not studied prior to their approval? For instance, biosimilar adalimumab is being stud-

ied in patients with RA and psoriasis, but will likely be extrapolated to use in inflammatory bowel disease (IBD), including both Crohn's and Ulcerative Colitis.

While it is unlikely that the FDA will be mandating post-approval registries for biosimilar agents, the collection of data across all of these disease states will be critical to inform society of their real world CER and CE. Collection of toxicities and side effects is expected to be

similar, but real world data will need to be collected to confirm and evaluate these outcomes across all of the indications and disease states for which they will be prescribed.

Fortunately, Corrona now has functioning disease registries in rheumatoid arthritis, psoriatic arthritis, spondyloarthropathies, psoriasis and inflammatory bowel disease. Thus, Corrona will be able to merge, and compare, these data sets and derive real-world insights on CER, CE and toxicities across all of the indications for biosimilars in a US population.

Finally, Corrona has completed a real world study of Comparative Effectiveness in the US examining TNF agents vs alternative biologics. Termed the CERTAIN trial, we prospectively collected DNA, RNA and multiple aliquots of serum and plasma at baseline and regular intervals after starting all of the present biological agents. Our deep clinical data were collected simultaneously with the biologic samples. The samples are stored at -80 degrees C and are now being used in collaboration with academic, and industry, investigators to examine the relationships, and evolution, of biomarkers, DNA and RNA to clinical response and toxicity. The potential for insights for improved targeting of these expensive interventions to patients who are biologically and genetically better suited to im-

prove with a particular drug has been a therapeutic goal for some time. Termed *personalised medicine*, we believe that the additional insights derived from our biobank of these samples will serve this field well and help derive insights into the nascent field of personalising biological medical interventions for complex immunologic diseases. A summary of the Corrona autoimmune disease registries, with categories and means of data collected is seen in Table II.

Corrona is also expanding into the realms of patient derived data from mobile device applications (Apps). Specific Apps are being developed for all of the disease states covered in our registries and we anticipate additional data on compliance, quality of life and attitudes regarding the acceptance of new drugs and a treat to target philosophy. These data sources will be used to inform an approach to deconstructing patient fears and reluctance to advance treatments in order to achieve low disease activity. Of note is that these real-time behavioural and attitudinal observations can be connected with patient disease as measured at the time of a clinic visit by their medical specialist. There will have to be an inherent value proposition for the patient, and Corrona believes that connecting subjects with their physician-derived data in a dashboard on their mobile App or home computer will be important to

keep them engaged. In addition, Corrona will be collecting data from large claims databases to identify possible events which could have been missed at the time of routine visits. A summary of the Corrona data collection sources is seen in Table III.

Corrona has evolved and expanded over the 15 years since our founding. We believe that the singular insights we can derive from the unique US population of drug users will continue to prove invaluable to society, treating physicians, payers, the pharmaceutical industry and of course the patients who suffer with chronic autoimmune diseases. We are continuously reevaluating and reworking our value proposition for all of our constituents in order to remain on the cutting edge of meaningful data collection and interpretation.

References

1. ASKLING J, FAHRBACH K, NORDSTROM B, ROSS S, SCHMID H: Cancer risk with tumor necrosis factor alpha inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept and infliximab using patient level data. *Pharmacoepidem and Drug Safety* 2011; 20: 119-30.
2. CURTIS JR, JAINA, ASKLING J *et al.*: A comparison of patient characteristics and outcomes in selected European and US rheumatoid arthritis registries. *Semin Arthritis Rheum* 2010 Aug; 40: 2-14.e1
3. KREMER JM, GREENBERG J: Interpreting registry derived drug studies: does societal context matter? Editorial. *Arthritis Rheum* 2009; 60: 3155-7.