Chinese registry of rheumatoid arthritis (CREDIT): I. Introduction and prevalence of remission in Chinese patients with rheumatoid arthritis

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Abstract

Objective

To introduce the Chinese Registry of rhEumatoiD arthrITis (CREDIT), which is the first nationwide, multicentre, online rheumatoid arthritis (RA) registry in China, and to depict major cross-sectional data and treatment strategies of Chinese RA patients.

Methods

RA patients who fulfilled the 2010 ACR / EULAR classification criteria for rheumatoid arthritis were recruited into the registry by their rheumatologists from 144 clinical centres in China. Data, including demographics, disease characteristics, co-morbidities, treatment, and adverse reactions, were collected and documented through the predefined protocol.

Results

8071 registered patients (F:M = 4.03:1) were registered up to May 2017. Mean age at symptom onset and at diagnosis was 46.15±14.72y and 48.68±14.54y, respectively. Point prevalence of remission (95% CIs) was 14.88% (14.10–15.66%), 4.23% (3.79–4.66%), 4.25% (3.81–4.69%), and 4.27% (3.83–4.72%) according to DAS28-CRP, CDAI, SDAI, and the 2011 ACR/EULAR remission criteria, respectively. 38.84% and 38.11% of treatment-naïve patients (n=3262) were in moderate (3.2<DAS28–CRP≤5.1) and high (DAS28-CRP>5.1) disease activity, respectively. Among treatment-naïve patients, those who were initiated on treatment with bDMARDs had higher disease activity than those who were treated with csDMARDs (p<0.05). Three months after initiating bDMARDs, 19.29% (n=38) of patients achieved remission (DAS28-CRP<2.6).

Conclusion

The CREDIT registry is an effective tool for real-world study of RA patients in China. By providing information for diagnosis and treatment regimen, the CREDIT registry can enhance the application of treat-to-target (T2T) strategy and improve patient outcomes in China.

Key words

arthritis, rheumatoid, registry, remission rate, treat-to-target

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Introduction

Rheumatoid arthritis (RA) is one of the common chronic inflammatory rheumatic diseases in China. Not only does it cause joint cartilage and bone destruction, but also extra-articular manifestations (mainly vasculitis and interstitial lung disease) and systemic co-morbidities, including cardiovascular diseases, fragile fracture, lymphoma and even increased overall mortality (1, 2). Clinically, it is also associated with progressive disability, early death, and increased socioeconomic costs (3).

Internationally, registries of RA have been established and maintained for about thirty years. These registries have enabled us to understand this chronic disease better in the real world, and have provided us with more information than controlled trials. Longitudinal observational registries, like CORRONA (the Consortium of Rheumatology Researchers of North America Registry), have provided a great deal of of real-world evidence on epidemiology, disease characteristics, and therapeutic approaches (4). Registries are either drug-based or disease-based, or both. Disease-based registries enrol patients diagnosed with a particular disease such as RA, while drug-based registies enrol patients with particular medications (5).

It was estimated that China had more than 5 million RA patients by 2013, which has been a severe burden to families and society (6). However, there is limited data about the current status of Chinese RA patients. CREDIT is the first nationwide, multicentre, online, disease-based RA registry in China. In this study, we introduced the CREDIT registry and reported baseline characteristics, point prevalence of remission and treatment regimens with both conventional synthesised DMARDs (csDMARDs) and biological DMARDs (bDMARDs) in Chinese RA patients.

Materials and methods

CREDIT Registry

Aimed at enhancing the application of the "treat-to-target (T2T)" strategy nationwide, CREDIT was established in November 2016, and was supported by the Chinese Rheumatism Data Center (CRDC) (7). Originating at Peking Union Medical College Hospital (PUMCH), the CREDIT registry currently has 144 participating medical centres that have covered all provincial administrative areas of mainland China. Setting-up this registry was approved by the IRB of PUMCH. This registry has been approved by each individual participating medical centre according to local regulations.

Patient recruitment

Up to May 2017, CREDIT had 8,701 registered RA patients, and enrolment had been increasing at a speed of 1,000 patients/month. All patients fulfilled the 2010 American College of Rheumatology (ACR)/the European League Against Rheumatism (EULAR) classification criteria (8) were recruited by trained rheumatologists. Patients were only enrolled after informed consent forms were signed by themselves or authorised guardians. There were no preferences for disease activity or insurance type.

Treatment-naïve patients were defined as either csDMARD-naïve (no history of receiving any csDMARDs nor bDMARDs before entering CREDIT) or bDMARD-naïve (no history of receiving any bDMARDs before entering, but might have ever been treated with csDMARDs). Patients initiated both csDMARDs and bDMARDs on entering were counted in the bDMARD-naïve group. In this way, there was no interaction between csDMARD-naïve and bDMARD-naïve patients.

Data collection

All CREDIT registry centres adopted the same pre-specified protocol for data collection. Each patient had a specific ID. Statistics experts and engineers were included to provide support on data analysis and management.

Main variables documented in the CREDIT registry included demographics, disease characteristics, disease activity indexes (DAIs), comorbidities, treatment and adverse effects (Table I). Variables were collected at baseline and every follow-up visit afterwards. Follow-up data also included time of the visit, updates on variables described

above, and other information if needed. The data were basically collected in three ways:

1. Self-report. Patients were encouraged to document patient-reported outcomes through mobile phone applications that could be downloaded free from major app stores such as AppStore and Google Play.
2. Chart upload or physician documentation. Physician-evaluated data (like TJC, SJC, and PhGA) were entered by rheumatologists.
3. Automated calculation. DAIs were calculated and recorded automatically according to given definition.

Remission criteria

RA disease activity was documented by the following indexes: Disease Activity Score-28 joints (DAS28-ESR and DAS28-CRP), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), and 2011 ACR / EULAR remission criteria. Similarly, remission was defined by DAS28-CRP<2.6, SDAI≤3.3, CDAI≤2.8, and fulfillment of the 2011 ACR/EULAR remission criteria.

Statistical analysis

After careful data review, 36 (0.41%) patients under 16 years old and 594 cases (7.08%) with incomplete core data were excluded from the data analysis. Continuous values were expressed as mean ± standard deviation (SD) or median (Inter-quartile range [IQR]) and categorical data were reported as the number of patients (percentage). The unpaired *t*-test was used for comparison between groups for continuous data and the chi-squared (χ^2) test was used to test significance for the contingency table analysis. SPSS (v. 23.0, SPSS Inc., IL, USA) was used for data analysis and a two-sided *p*-value less than 0.05 was considered statistically significant.

Results

Demographics

6464 (80.09%) patients were female. Median (IQR) disease duration was 3.86 (1.12–9.99) years. 83.74% of patients were RF or anti-CCP positive. Mean age at symptoms onset and diagnosis was 46.15±14.72 (range 1.34–95.4) y, and 48.68±14.54 (range 1.34–95.2) y, respectively.

Remission rate

Of all included patients, cross-sectional remission rate (95% CIs) were 14.88% (14.10–15.66%), 4.23% (3.79–4.66%), 4.25% (3.81–4.69%), and 4.27% (3.83–4.72%) for DAS28-CRP, CDAI, SDAI, and the 2011 ACR/EULAR remission criteria, respectively.

Treatment strategies

The proportions of patients receiving glucocorticoids (GCs), methotrexate (MTX), leflunomide (LEF), combined csDMARDs (neither MTX nor LEF), and bDMARDs were 39.54%, 53.83%, 40.4%, 30.93%, and 8.55%, respectively. We retrospectively assessed efficacy of bDMARDs, including tocilizumab (TCZ) and tumour necrosis factor-α inhibitors (TNFi) in combination with csDMARDs. 298 patients who received TCZ (n=61) or TNFi (n=237) for more than 3 months before entering the CREDIT registry were identified. Overall, 84 (28.2%) patients achieved remission (DAS28-CRP <2.6) three months after initiating bDMARDs.

Characteristics of treatment-naïve patients

Of 3262 treatment-naïve patients (definition in *Methods*, also Table II), 80.0% were female and mean disease duration was 3.21y (IQR, 1.03–9.03y). As with disease activity, 38.84% (95% CI 31.1–34.1%) and 38.11% (36.4–39.8%) of them were in moderate (3.2<DAS28–CRP≤5.1) and high (DAS28-CRP>5.1) disease activity, respectively. As for subgroup studies, patients treated with bDMARDs had higher disease activity than those treated with csDMARD group ($p<0.05$).

Table I. The main variables collected in the CREDIT registry.

Demographics
- Age, gender, height, weight
- Family history of rheumatic disease, tobacco use
- Marital status, educational level, career, household income

Disease characteristics
- Year (month) of symptom onset
- Year (month) of diagnosis
- Initial fulfillment of 1987 ACR classification criteria
- Rheumatoid factor (RF)
- Anti-citrullinated protein antibodies (anti-CCP)
- Erythrocyte sedimentation rate levels (ESR)
- C-reactive protein levels (hsCRP)
- Morning stiffness (minutes)
- Tender joint count (TJC, 28 and/or 44 joint)
- Swollen joint count (SJC, 28 and/or 44 joint)
- Patient global assessment (PtGA)
- Physician global assessment (PhGA)
- VAS for pain, fatigue (0-10 scale)
- Complete blood count, comprehensive metabolic panel
- Imaging (ultrasound, x-ray, and MRI)
- Bone mineral density (optional)
- HAQ (optional), SF-36 (optional)

Disease activity index
- DAS28 (DAS28-ESR, DAS28-CRP)
- Simplified Disease Activity Index (SDAI)
- Clinical Disease Activity Index (CDAI)
- 2011 ACR/EULAR criteria

Comorbidities
- Cardiovascular disease
- Stroke
- Fragility fracture
- Joint replacement
- Tumour

Treatment
- Drugs (type, brand, dose, frequency, start and end date, reason of ending)
- Intra-articular injections

Adverse effects
- Infection
- Abnormal liver/kidney function tests
- Gastrointestinal reaction
- Rash
- Headache or dizziness
- Bone marrow suppression

Discussion

Report on the remission rate of Chinese RA patients is limited. In our study (14.88%, 95% CI [14.10–15.66%], defined by DAS28-CRP), remission rate is different from another cross-sectional survey in which 486 patients (8.6%) were involved (9). With more enrolled patients, more sites spread across the country and more advanced technology to collect real-world data, data in our registry are more representative. Remission rates around the world ranges from 22% (IORRA registry, Japan) (10) to 51% (ESPOIR registry, France) (11) based on DAS28-CRP. Our remission rate is lower compared to other populations.

High disease activity at baseline is a prominent feature of this registry. More than three quarters of all treatment-naïve patients were in moderate or high

Table II. Characteristics of naïve patients in the CREDIT registry.

	All	csDMARD-naïve	bDMARD-naïve
Patients, *n*	3262	2987	275
Age, mean ± SD	52.5±13.1	52.4±13.0	53.2±13.8
Female, %	80.0%	80.3%	77.1%
Duration/y, median (IQR)	3.21 (1.03-9.03)	3.07 (0.05-4.51)‡	4.83 (1.01-8.89)‡
RF or CCP positive, %	84.7%	84.8%‡‡	84.0%‡‡
PhGA (0-10 scale), mean ± SD	5.2±2.6	5.2±2.6	5.1±2.7
PtGA (0-10 scale), mean ± SD	5.4±2.4	5.4±2.4	5.6±2.4
ESR (mm/h), median (IQR)	35.0 (18.0-64.0)	34.0 (18.0-62.0)	44.0 (22.0-76.0)
CRP (mg/L), median (IQR)	12.3 (3.7-34.8)	12.3 (3.69-34.8)	18.6 (4.8-47.8)
SJC (44 joint count), mean (range)	0.63 (0-36)	0.64 (0-36)	0.48 (0-22)
TJC (44 joint count), mean (range)	0.64 (0-42)	0.65 (0-42)	0.52 (0-27)
Comorbidities			
Cardiovascular disease, %	1.4%	1.4%	2.2%
Stroke, %	1.1%	1.0%	1.8%
Fragility fracture, %	1.3%	1.1%	2.9%
Joint replacement, %	0.9%	0.7%	2.9%
Tumour, %	0.4%	0.4%	0
Mean Disease Activity Index			
DAS28-CRP, mean±SD	4.55 ± 1.64	4.54 ± 1.64	4.66 ± 1.68
CDAI, median (IQR)	26.0 (14.5-42.5)	25.7(14.4-41.3)‡‡	31.5 (17.4-58.0)‡‡
SDAI, median (IQR)	28.7 (16.2-46.3)	28.3 (16.0-45.1)‡‡	34.2 (19.1-61.5)‡‡

‡ $p<0.01$; ‡‡ $p<0.001$; otherwise, no significant difference.
csDMARDs: conventional synthesised DMARDs; bDMARDs: biologic DMARDs; SD: standard deviation; IQR: interquartile range; RF: rheumatoid factor; CCP: anti-citrullinated protein antibodies; PhGA: physician global assessment; PtGA: patient global assessment; ESR: erythrocyte sedimentation rate levels; CRP: C-reactive protein; SJC: swollen joint counts; TJC: tender joint counts.

disease activity (38.84%, 38.11%, respectively). There is a directly proportional relationship between MDA/HDA and physical dysfunction (1, 12), joint destruction (13), and a 7–11 times less chance to achieve clinical remission (11). Relationship between disease activity and duration, treatment approaches for MDA/HDA patients, and factors affecting patients achieving remission or low disease activity should be explored by further studies.

Baseline remission rate cannot reflect the efficacy of treatments. With the effort to apply treat-to-target strategy in China for years, 53.83% of patients received MTX at baseline. Naïve patients initiating bDMARDs had significantly higher disease activity than patients initiating csDMARDs. Patients who have failed csDMARDs treatment or with higher disease activity received bDMARDs, which is in accordance with recommendations of international task force (14).

Retrospective analysis showed that 3 months after initiating bDMARDs, 28.2% of patients achieved remission. This is evidently different from remission rate of the whole population of CREDIT, which indicates applying bDMARDs is beneficial for achieving remission in Chinese RA patients. Either MTX monotherapy, or combination therapy with bDMARDs, standardised therapies have contributed to higher remission rate. Use of bDMARDs are greatly limited by their costs, especially in dose escalated patients (15). Good news is that Etanercept will be covered by Chinese government medical insurance from September 2017. After 3–6 months of csDMARDs treatment, RA patients whose disease activity decrease is less than 50% of baseline disease activity can get reimbursement from governmental medical insurance for bDMARDs usage.

Despite the strength of the sample size and pre-specified multicentre longitudinal design, our study has several limitations. This study only demonstrates cross-sectional remission rate, which cannot reflect changes during follow-up and cannot reveal the efficacy of treatment strategies. However, this point remission rate is only the first step in an RA cohort study in China. Only six months after it was set up, the CREDIT cohort already has more than 8,000 registered patients, and has provided us with a great deal of information about current status, including disease activity, comorbidities, treatment strategies, and adverse effects of RA patients in China.

In conclusion, the CREDIT registry has portrayed the main characteristics of RA patients in China since its establishment. With this large and developing cohort of patients, CREDIT may enable us to understand the 'real-world' situation of Chinese RA patients, which will promote early diagnosis and improve patients' long-term prognosis, and eventually facilitate the application of treat-to-target strategy in Chinese RA patients.

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