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ORIGINAL ARTICLE

The incidence rate and the early management of rheumatoid arthritis in Slovenia

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Abstract

Epidemiological data for rheumatoid arthritis (RA) differ according to ethnicity and geographical region. Moreover, despite of clear RA management guidelines, the implementation of treat-to-target (T2T) strategy often remains incomplete. Our objectives were to determine the incidence rate of RA, the clinical characteristics, and the level of adherence to the T2T guidelines in Slovenia. We analyzed prospectively the collected data of adult patients diagnosed with RA from 2014 through 2016 at the Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia. The department provides rheumatology services to a well-defined region with a population of 704,000 adult residents. During the 3-year observation, we identified 341 incipient cases of RA (75% females, median (IQR) aged 64 (52.0–75.4) years), resulting in an annual incidence rate of 16.1 per 100,000 adults (95% CI 14.5–17.9). The incidence rate peaked in the 70–79-year age interval. The median time from the onset of symptoms suggestive of RA to rheumatology consultation was 12.9 (4.4–26.1) weeks, and the median time from referral to consultation was 1 (1–3) day. Within 12 weeks of symptom onset, 161 (47.2%) incipient RA patients were examined by a rheumatologist, and 123 (36.1%) were started on DMARD therapy. The estimated incidence rate was in line with the available epidemiological data. Our early interventional clinic enabled us to identify and manage a substantial portion of RA patients within the recommended time frame.

Keywords Incidence · Management · Referral · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases. Most epidemiological studies in RA stem from Western countries, suggesting a prevalence of RA in the range of 0.3–1.0% in Caucasian individuals [1, 2] and an incidence rate of 24–45 per 100,000 person years [3]. However, the prevalence of RA differs between ethnicities as well as geographically. For example, a lower prevalence has been reported in Southern Europe compared to Northern Europe [1]. There have also been conflicting data regarding a possible RA incidence decline in recent years [4, 5].

While no cure exists, early diagnosis and treatment of RA may at least limit its progression [6, 7]. If RA patients are treated very early in the course of the disease, the chances of achieving disease remission and avoiding joint damage are improved [8–10]. This so-called *window of opportunity* is believed to lie within the first 12–20 weeks after symptom onset [8, 9]. Thus, it is essential to recognize the arthritis within this time frame.

However, the implementation of clinical guidelines can be challenging and significant proportion of patients still fails to be recognized and treated within the proposed time frames [11]. In Slovenia, epidemiological data regarding RA are lacking. Moreover, the number of rheumatologists per capita is 40% lower than the European Union average, which makes the implementation of management guidelines even more challenging. The aim of the current study was therefore to determine the incidence of RA and the characteristics of early RA management in Slovenia.

Rok Ješe and Katja Perdan-Pirkmajer contributed equally to this work.

Rheumatology in Slovenia: Clinical practice and translational research

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Methods

Patients and setting

This was a prospective observational study conducted from 1 January 2014 to 31 December 2016 at the Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia. Our Rheumatology Department is an integrated secondary/tertiary teaching hospital that provides rheumatology services for a population of more than 704,000 of 1,700,000 adult (i.e., ≥ 18 years old) residents of Slovenia. The patients are referred to our department by general practitioners or other specialists. We have an early interventional clinic where patients considered urgent by the referring doctor, reach a rheumatologist within 24 h from the referral from Monday through Friday, excluding national holidays. We collected data on incipient adult cases of RA diagnosed from 2014 through 2016. The diagnosis was established on the basis of the clinical picture and laboratory investigations including immuno-serology. We excluded from further analyses the cases in which during the first 6 months of follow-up, another cause of arthritis than RA was diagnosed. From the paper and the electronic medical records, we extracted patients' demographics, dates of symptom onset, referral to a rheumatologist, initial rheumatological assessment, diagnosis, DMARD initiation, swollen joint counts (SJC), tender joint counts (TJC), erythrocyte sedimentation rate (ESR), patient and evaluator global assessments, C-reactive protein (CRP), rheumatoid factor (RF), and anti-citrullinated peptide antibody (ACPA) status, and the fulfillment of the ACR/EULAR 2010 RA classification criteria [12], date, kind and dose of the initial DMARD, and smoking history. The disease activity was assessed by DAS 28-ESR-3v, DAS 28-CRP-3v, because the patient and evaluator global disease activity assessments were not available in all patients at the initial visits.

Statistical analysis

The incidence rate for RA was calculated by dividing the data on new disease onsets (numerator) and ((average population size) × (duration of follow-up)) as denominator. The crude incidence was standardized to the 2016 population data in Slovenia. Incidence rates based on gender and different age groups were also calculated. As for RA characteristic in our observed cohort, patients were separated into the ACPA positive and ACPA-negative group and an analysis of possible differences between those two groups were performed.

Next, the early management analysis was performed by using recorded dates to calculate the time from the symptom onset to referral, first rheumatologic assessment, diagnosis, and DMARD initiation. The initial DMARD dose was also analyzed. The percentage of patients assessed by a rheumatologist and/or treated with a DMARD within 12 weeks of symptom onset and the median times for delay were then calculated.

The clinical data were analyzed using MedCalc version 14. The independent-samples Mann-Whitney *U* test was used for the metric variables, and a Mid-*P* exact test was used to analyze the categorical variables. *P* values less than 0.004 were regarded as statistically significant (original *P* value 0.05 adjusted for multiple testing using the Bonferroni correction). For incidence confidence interval calculations, a one-sample Poisson rate was used, MiniTab v18, Inc. USA.

Patient consent and ethics committee approval

Patient consent was not needed since the collected data stems from routine clinical practice. The study was approved by the Republic of Slovenia National Medical Ethics Committee.

Results

Incidence rates

Between 1 January 2014 and 31 December 2016, we identified 341 incipient cases of RA (75.1% females, median age 64 (IQR 52.0–75.4) years), resulting in an estimated annual incidence rate of 16.0 1 per 100,000 adults (95% CI 14.5–17.9), in females 23.6 (95% CI 20.8–26.7) per 100,000 and in males 8.3 (95% CI 6.6–10.2) per 100.000, and a female to male ratio of 2.8. The incidence rate increased with age in women and men until it peaked in the 70–79-years age interval (Fig. 1). The incidence rate in this age group was 53.5 and 27.4 per 100,000 females and males, respectively. The female to male ratio in this age group was 1.9. After the age of 80 years, the incidence rate decreased.

Patient characteristics

Among the 341 new RA cases, 323 (94.7%) fulfilled the ACR/EULAR 2010 classification criteria [12]. More than 70% were ACPA positive. Overall, the ACPA-positive patients were significantly younger and more likely ever smokers; they were found to have lower disease activity at presentation (including swollen/tender joint counts and CRP) than their ACPA-negative counterparts (Table 1).

Management characteristics

Most patients (78.6%) were referred to our early interventional clinic. Within 12 weeks of symptom onset, 161 (47.2%) new RA patients were examined by a rheumatologist, and 123 (36.1%) were started on DMARD therapy. The time intervals are presented in Table 2.

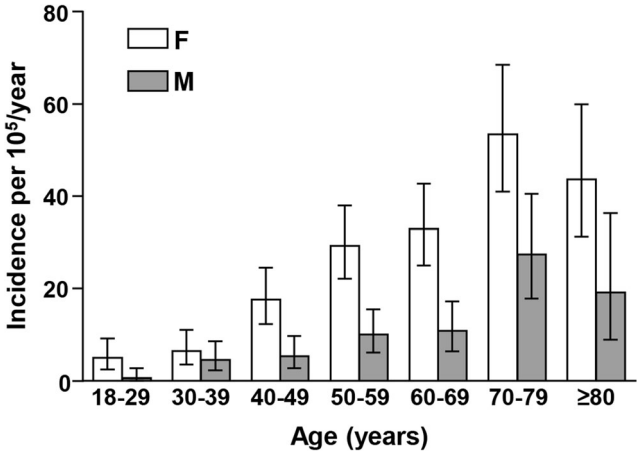

Fig. 1 Age stratified gender-specific incidence of RA in Slovenia. Data are given as incidence rates ± 95% confidence interval

As a part of the initial treatment strategy, 84% patients received glucocorticoids (55% by intramuscular injections, 24% per os, and the rest intra-articularly or intravenously) and 78% patients were started on methotrexate (Fig. 2a). In 86% patients, the MTX starting dose was 15 mg (Fig. 2b).

Discussion

Existing epidemiological studies have demonstrated a variable incidence and prevalence in different populations [1]. We report the RA incidence rate in a well-defined region in Slovenia for the first time. As the Slovenian population is demographically homogenous, we assume the incidence figures are representative of the entire country. Based on our data, we estimate that the annual incidence in Slovenia is 16.0 (females 23.6, males 8.3) per 100,000 adults which is in line with other reports from Southern Europe [1]. These numbers are lower than in Northern Europe, where between 20 and 50 new RA cases per 100,000 are expected [3]. However, data on regional variations are also contradictory, as two studies from different European regions, namely Italy and Sweden, both with a similar epidemiologic approach, reported fairly similar incidences: 35 per 100,000 in Italy vs 41 per 100,000 in Sweden [13, 14]. A study from Spain reported an incidence rate of 25 per 100,000 which is closer to our estimates [15] taking into consideration that they included patients aged > 16 years, while our sample included subjects ≥ 18 years of age.

Some studies indicated a possible decrease in the RA incidence. For instance, a nationwide population-based study recently performed in the UK observed a declining incidence with currently 38 new RA cases per 100,000 person years [5]. Also, in the cohort from Minnesota, the RA incidence had been monitored since the 1960s and it apparently declined from the initial value of 60 per 100,000 to 41 in 2005 [4].

One must tread carefully when interpreting or comparing results of different studies as methodologies may differ considerably. While we prospectively examined all subjects referred to our secondary/tertiary (and the only regional) rheumatology center during the 3-year period, the Italian and Swedish data were mostly administrative, based on data from comprehensive databases in 2011, and from 2006 through

Table 1 Demographic and clinical features of RA patients

	All	ACPA+	ACPA−	*P* value
No. of patients (% of all)	341	253 (74%)	88 (26%)	N/A
Male (*n*, %)	85 (25)	61 (72)	24 (28)	0.55
Age, years	64.0 (52.0–75.4)	60.5 (IQR)	71.2 (IQR)	0.0001
Smokers (ever) [*n* = 252], # (%)	109/252 (43.2)	93/189 (49)	16/63 (25)	0.0009
Patients fulfilling 2010 ACR/EULAR classification criteria for RA, # (%)	323 (94.7)	246 (97)	77 (87)	0.0014
DAS28-ESR-3v	4.9 (4.1–6.1)	4.8 (3.9–5.6)	5.9 (4.8–6.8)	< 0.0001
DAS28-CRP-3v	4.4 (3.6–5.6)	4.1 (3.9–4.4)	5.4 (5.1–5.9)	< 0.0001
SDAI [*n* = 211]	28 (18–43)	26(23–28)	40 (33–44)	< 0.0001
CDAI [*n* = 211]	26 (17–38)	23 (20–26)	34 (29–40)	< 0.0001
CRP, mg/l	16.0 (7.0–48.0)	14.0 (5.0–46.0)	25.5 (11.5–51.5)	0.0036
ESR, mm/h	39 (24–55)	39 (23–55)	41 (25–43)	0.5416
SJC (28 joints)	6.0 (2.0–5.5)	5.0 (2.0–9.0)	12.0 (7.0–16.0)	< 0.0001
TJC (28 joints)	5.0 (2.0–13.0)	4.0 (2.0–10.0)	12.0 (4.0–19.0)	< 0.0001
RF positive, *n* (%)	241 (71)	217 (86)	24 (11)	< 0.0001

Except where indicated otherwise, values are medians (interquartile range). *n* = 341 if not indicated otherwise; *RA*, rheumatoid arthritis; *ACPA*, anti-citrullinated peptide antibody; *N/A*, not available; *RF*, rheumatoid factor; *DAS28-ESR-3v*, DAS28 with erythrocyte sedimentation rate-three variables; *DAS 28-CRP3v*, DAS28 with CRP-three variables; *SDAI*, simple disease activity index, *CDAI*, clinical disease activity index; *SJC*, swollen joint count; *TJC*, tender joint count

Table 2 RA management time frames in Slovenia

Time interval	Duration
Symptom onset to first rheumatologist assessment [weeks]	12.7 (4.4–26.1)
Referral to first rheumatologist assessment [days]	1.0 (1–3)
Symptom onset to diagnosis [weeks]	13.1 (6.3–28.9)
Time from symptom onset to glucocorticoid initiation [weeks]	13.0 (5.8–27.2)
Time from symptom onset to DMARD initiation [weeks]	16.1 (8.6–32.8)

Values given as medians (interquartile range)

2008, respectively [13, 14]. The Spanish estimates were also register based, but came from the primary care registries [15]. There were also differences in the population samples used, as our region covers approximately 40% of Slovenia's adult population, in contrast to, e.g., the Italian study which was done using data from almost 5 million patients, which represents approximately 8% of the national adult population. Methodological differences aside the age-related incidence rate were mostly comparable across the studies. The incidence of RA peaks in the late seventh to early eighth decade of life and with an age-dependent decrease of the female to male ratio. With aging of the population in Slovenia, our data imply that the prevalence of patients with RA might increase.

As expected, there were more females than males in our cohort. Most of our patients were ACPA positive and RF positive, and a fifth was negative for both autoantibodies. Most smokers were in the ACPA-positive group, which is also consistent with the proposed association between tobacco use and RA; the link is strongest or even restricted to ACPA-positive disease [16]. In line with previously reported observations, the ACPA-negative group in our study presented with a higher disease activity, a higher number of affected joints and higher CRP levels [17]. Boer and coworkers recently showed that, when patient-related outcomes, such as physical functioning and restrictions at work are considered, ACPA-negative patients fare as poorly or poorer than ACPA-positive counterparts, which have been shown to have a more severely progressive disease [18]. This implies that the effort to further improve the course of the disease should be proportional in all RA patients [19].

Evidence accumulated over the past decade suggests that there are two main anchors of successful RA management: early detection and intensive therapeutic approaches. Ideally, the diagnosis should be made no later than 12 weeks after the onset of symptoms, and the disease treatment aiming for achieving and maintaining RA remission [20]. In clinical practice, a timely assessment of patients with new onset RA is often challenging. In Europe, the median delay from symptom onset to patients seeing a rheumatologist across ten centers was 24 weeks [21]. Our early interventional clinic, where most of incipient RA patients are referred to, enabled us to cut down the median time intervals from symptom onset to rheumatologist assessment, diagnosis, and treatment closer to the recommendations (median time of 12.7, 13.2, and 16.6 weeks respectively), which were shorter than those reported by Raza [21]. Despite the heavily protracted waiting times for the first rheumatology appointment in Slovenia, 47% of our early RA patients are examined by rheumatologists within 12 weeks of symptom onset, and 36.1% were started on DMARD therapy in this time frame. These data are similar to those reported in an Austrian study, where a rapid access clinic in the private sector resulted in a substantial improvement of access to rheumatologists [22]. As recommended by the current RA management guidelines [7], almost 80% of patients received MTX as their first DMARD, mostly 15 mg per week to start with. This was combined with different regiments of glucocorticoids in over 80% of patients. Clearly, there is still room for improvement, as more than 50% of patients still miss their window of opportunity. As the median time from referral to rheumatologist's assessment was 1 day, improvements will

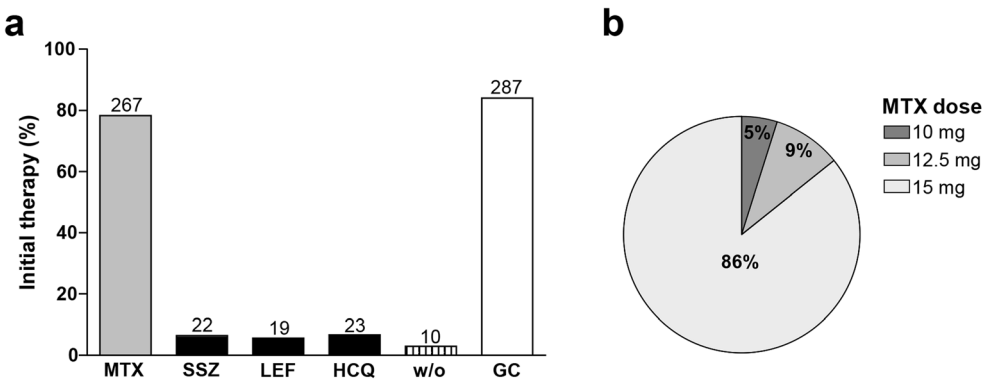

Fig. 2 Characteristics of initial DMARD treatment in RA patients in Slovenia. **a** Percentage of different synthetic DMARDs used. **b** Percentage of different MTX starting dose used. MTX, methotrexate; SSZ, sulphasalazine; LEF, leflunomide; HCQ, hydroxicloroquine; w/o, without therapy; GC, glucocorticoids

have to be achieved on part of the patients' awareness and on part of the general practitioners' referral speed.

The major strengths of our study were the excellent conditions for the enrollment of patients stemming from the national health insurance that ensures free access to primary, secondary, or tertiary care to all Slovenian residents. Considering the design of our study, inclusion of about 40% of the national population and the ethnical homogeneity of the Slovenian population, we believe that the incidence rate data have a good external validity for the entire Slovenian population.

One might argue that there exists a possibility of underestimating the incidence rate as some residents of the investigated regions might have been diagnosed and managed at other rheumatology centers in the country. We believe this to be unlikely, as not all rheumatology centers in Slovenia have an early intervention clinic and are further supported by the observation by the constant influx of patients from other regions to our center exactly due to the short waiting times for urgent referrals at our center. We admit, however, that we can only vouch for the internal validity of the findings on the management of RA, while its external validity cannot be guaranteed due to the potential differences in the accessibility of early rheumatology assessment in other Slovenian centers.

To conclude, we estimated the RA incidence rate at 16.0 per 100,000 adults in Slovenia, which was comparable to the rest of Southern Europe. Additionally, we characterized the clinical picture of RA at presentation and showed that despite the shortage of rheumatologists, a considerable proportion of RA patients was managed within the window of opportunity and in accordance with the current guidelines.

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Compliance with ethical standards

The study was approved by the Republic of Slovenia National Medical Ethics Committee.

Disclosures None.

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