Rheumatoid Arthritis in a North American Native Population: Longitudinal Followup and Comparison with a White Population

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ABSTRACT. ***Objective.*** To describe differences in phenotype and outcomes in North American Native (NAN) patients with rheumatoid arthritis (RA) followed prospectively and compared to white patients with RA.

Methods. Patients from a single academic center were followed over 20 years using a custom database. Data included diagnoses, year of disease onset, ethnicity, modified Health Assessment Questionnaire (mHAQ) score, patient and physician global scores, tender and swollen joint counts, treatment, serology, and erythrocyte sedimentation rate (ESR). Records of all white (n = 1315) and NAN (n = 481) patients with RA were abstracted. Cumulative treatment data and clinical measures were compared.

Results. Disease duration was longer in white patients compared to NAN patients (16 ± 11 vs 14 ± 10 years, respectively; p = 0.03). Onset age was 34 years for NAN patients and 43 years for white patients (p < 0.001). NAN patients were more frequently positive for rheumatoid factor (89% vs 74%; p < 0.001) and antinuclear antibody (57% vs 21%; p < 0.001). Although mean tender joint counts and swollen joint counts were similar, NAN patients had higher Lansbury scores (weighted joint count; 66.5 vs 49.7; p < 0.001), mHAQ scores (1.1 vs 0.9; p = 0.001), and ESR (31 vs 25 mm/h; p < 0.012). NAN patients had more frequent knee (53% vs 34%; p < 0.001) and elbow (62% vs 48%; p = 0.007) involvement. Compared to white patients, NAN patients took a higher lifetime number of disease-modifying antirheumatic drugs (3.2 ± 1.9 vs 2.2 ± 1.7; p < 0.001), had more combination therapy (38% vs 29%; p = 0.002), and had more frequent prednisone use (55% vs 39%; p < 0.001).

Conclusion. Compared to white patients, NAN patients with RA develop disease earlier, are more frequently seropositive, have greater large joint involvement, and greater disease burden, although treatment is more aggressive. These differences are present early and persist throughout the disease course. (J Rheumatol First Release June 15 2010; doi:10.3899/jrheum.091452)

Key Indexing Terms:
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North American Natives (NAN) have some of the highest documented prevalence rates of rheumatoid arthritis (RA) in the world, ranging from 2% to 5%, in diverse populations scattered across the continent[1,2,3,4,5,6,7,8]. A higher frequency of juvenile onset arthritis in NAN is also reported[9,10,11]. There are also reports of higher than expected frequency of rheumatoid factor (RF) and antinuclear antibodies (ANA) in NAN populations; both RF and ANA are known to be markers of severe, chronic disease[12,13].

Despite these documented differences, information on phenotype, clinical course, and outcomes in NAN patients with RA is lacking. Several studies suggest severe disease, with a high frequency of erosions[14,15], deformity[8], and disability[3,16,17]. There are few detailed reports, little information on treatment, and no studies including a control population.

We report the first description of clinical course and outcomes in a large cohort of NAN patients with RA followed prospectively over several years compared to a large cohort of white patients with RA followed at the same center. Manitoba NAN peoples are primarily Cree, Ojibway, and Metis, with smaller populations of Dakota, Dene, Sioux, and

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Chipewyan people. Approximately 14% of the Manitoba population self-identifies as NAN[18].

MATERIALS AND METHODS

The University of Manitoba Arthritis Centre (UMAC) has been maintaining a prospective, longitudinal database for clinical and research purposes on all patients seen at the center since 1990. Patients were cared for by a small group of 3–6 rheumatologists over the years of data collection. The UMAC database includes the patients' diagnoses, year of disease onset, and date of first and each subsequent visit to the Arthritis Center. All diagnostic labels are assigned according to whether patients meet current clinical criteria, and are overwritten if the diagnosis changes. Patients are assigned a diagnosis of RA only if they have met the American College of Rheumatology 1987 revised criteria[19]. The database also includes self-reported data on ethnicity, education, and occupation. At each visit, patients complete a modified Health Assessment Questionnaire (mHAQ) and visual analog scales (VAS) for pain, fatigue, and global disease activity (GDA). Physicians complete tender and swollen joint counts, physician global VAS, and current treatment information, and update serology and acute-phase reactants, if performed. The computerized database program calculates a Lansbury Index, a weighted joint count that takes into account the size of the affected joint[20,21], for each clinic visit. RF and ANA are generally obtained at the baseline visit, and subsequently repeated if clinically warranted. RF is performed by nephelometry. ANA is measured using immunofluorescence and ELISA. Anticyclic citrullinated antibody (anti-CCP) was not clinically available at the start of data collection, and is therefore not included in this dataset. The database contains records of 8003 patients with rheumatic diseases as of February 28, 2008.

Records of all patients with a diagnosis of RA or juvenile RA who had self-identified as being of either white or NAN background were abstracted. The 2 cohorts were further divided into those with disease duration of 5 years or less (Cohort 1), between 5 and 15 years (Cohort 2), and greater than 15 years (Cohort 3). For each cohort, age of onset, serology, cumulative treatment data, acute-phase reactants, mHAQ scores, VAS scores, and tender and swollen joint counts and Lansbury scores were compared. Since this is a clinical database, the number of and intervals between clinic visits varied between patients; therefore we have chosen to present mean values and values at the last clinical assessment for these measurements.

Statistical analyses. Analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Descriptive analyses of the differences between the 2 ethnic groups were performed with the chi-squared distribution for categorical variables and with t-test for comparison of means for continuous variables.

RESULTS

Records of 481 NAN and 1315 white patients with RA were abstracted. Of these, 348 were in Cohort 1, 627 in Cohort 2, and 801 in Cohort 3. Gender distribution was not different; close to 80% of both groups in all cohorts were women. General and individual cohort characteristics are found in Table 1. The mean age at disease onset was 34 years in NAN patients (SD ± 14) compared to 43 years (SD ± 17) in white patients ($p < 0.001$). NAN patients were more frequently positive for RF and ANA (89% vs 74%, respectively, $p < 0.001$; and 57% vs 21%, $p < 0.001$). Mean RF titers were also more than twice as high in NAN patients compared to whites (775 IU/ml SD ± 1859 in NAN patients compared to 361 IU/ml SD ± 558 in white patients; $p < 0.001$; normal values in our laboratory are < 20 IU/ml). The proportion of patients positive for RF rose slightly with increasing disease duration in both ethnic groups, while the proportion of patients who were ANA-positive increased markedly with disease duration in both groups, but particularly in NAN patients: 71% of NAN patients vs 32% of whites in those with disease duration > 15 years were positive for ANA; $p < 0.001$ (Table 1).

Table 1. Selected demographics of North American Native (NAN) and white cohorts. Total n = 1796.

Characteristics	NAN, n = 481	White, n = 1315	p
Entire cohort			
Onset age, yrs ± SD	34 ± 14	43 ± 17	< 0.001
Disease duration, yrs ± SD	14 ± 10	16 ± 11	0.03
Female, % (n)	79 (380)	78 (1026)	NS
RF positive, % (n)	89 (428)	74 (973)	< 0.001
RF titer, mean IU/ml ± SD	775 ± 1859	361 ± 558	< 0.001
ANA positive, % (n)	57 (274)	21 (276)	< 0.001
Cohort 1, n = 348	104	244	
Onset age, yrs ± SD	39 ± 13	53 ± 16	< 0.001
Disease duration, yrs ± SD	3.0 ± 1.5	3.0 ± 1.4	NS
Last visit age, yrs ± SD	41 ± 14	53 ± 17	< 0.001
RF positive, % (n)	86 (89)	68 (166)	0.011
ANA positive, % (n)	38 (40)	19 (46)	0.007
Cohort 2, n = 647	188	459	
Onset age, yrs ± SD	36 ± 14	47 ± 16	< 0.001
Disease duration, yrs ± SD	9 ± 2.7	10 ± 2.8	NS
Last visit age, yrs ± SD	45 ± 14	56 ± 16	< 0.001
RF positive, % (n)	89 (167)	75 (344)	0.001
ANA positive, % (n)	53 (100)	23 (106)	< 0.001
Cohort 3, n = 801	189	612	
Onset age, yrs ± SD	29 ± 14	36 ± 16	< 0.001
Disease duration, yrs ± SD	24 ± 7	25 ± 9	NS
Last visit age, yrs ± SD	53 ± 13	61 ± 15	< 0.001
RF positive, % (n)	91 (172)	75 (459)	< 0.001
ANA positive, % (n)	71 (134)	32 (196)	< 0.001

RF: rheumatoid factor; ANA: antinuclear antibodies.

NAN patients reported significantly higher pain, fatigue, and GDA VAS in all 3 cohorts compared to white patients (Table 2). In Cohort 1, mean scores were about 10–15 mm higher for NAN patients compared to white patients (pain VAS 50 mm vs 39 mm, respectively, $p < 0.001$; fatigue VAS 55 mm vs 45 mm, $p = 0.002$; and patient GDA VAS 45 mm vs 31 mm, $p < 0.001$), and remained significantly higher for NAN patients in Cohorts 2 and 3 (Table 2). Mean physicians' GDA VAS scores were also significantly higher for NAN patients in all 3 cohorts (29 mm vs 22 mm in Cohort 1, $p = 0.002$; 25 mm vs 20 mm in Cohort 2, $p < 0.001$; and 26 mm vs 22 mm in Cohort 3, $p < 0.001$). Mean erythrocyte sedimentation rates (ESR) were about 5 mm/h higher in NAN patients compared to whites in all 3 cohorts (32 mm/h vs 23 mm/h in Cohort 1, $p = 0.02$; 30 mm/h vs 25 mm/h in Cohort 2, $p = 0.003$; and 30 mm/h vs 24 mm/h in Cohort 3, $p = 0.02$; Table 2).

Differences in functional limitations (mHAQ scores) varied among the 3 cohorts. Mean mHAQ scores were similar in those with early disease (Cohort 1, 0.58 in NAN patients

Table 2. Disease activity and functional status. Patient total n = 1796. All scores are mean ± SD.

Disease Activity Measure	NAN, n = 481	White, n = 1315	p
Cohort 1, n = 348	104	244	
mHAQ score	0.58 ± 0.47	0.47 ± 0.42	NS
mHAQ score at last visit	0.90 ± 0.69	0.67 ± 0.53	0.002
Fatigue VAS, 100 mm	55 ± 22	45 ± 23	0.002
Pain VAS, 100 mm	50 ± 23	39 ± 21	< 0.001
Patient Global Disease Activity VAS, 100 mm	45 ± 25	31 ± 20	< 0.001
MD Global Disease Activity VAS, 100 mm	29 ± 18	22 ± 13	0.002
ESR mm/h	32 ± 31	23 ± 20	0.02
Cohort 2, n = 647	188	459	
mHAQ score	0.72 ± 0.47	0.56 ± 0.49	< 0.001
mHAQ score at last visit	1.19 ± 0.69	0.86 ± 0.68	< 0.001
Fatigue VAS, 100 mm	50 ± 20	45 ± 23	0.01
Pain VAS, 100 mm	48 ± 18	39 ± 20	< 0.001
Patient Global Disease Activity VAS, 100 mm	40 ± 18	30 ± 19	< 0.001
MD Global Disease Activity VAS, 100 mm	25 ± 12	20 ± 10	< 0.001
ESR mm/h	30 ± 21	25 ± 21	0.003
Cohort 3, n = 801	189	612	
mHAQ score	0.77 ± 0.50	0.72 ± 0.52	NS
mHAQ score at last visit	1.21 ± 0.70	1.02 ± 0.72	0.003
Fatigue VAS, 100 mm	53 ± 21	49 ± 22	0.030
Pain VAS, 100 mm	51 ± 18	45 ± 20	< 0.001
Patient Global Disease Activity VAS, 100 mm	40 ± 18	33 ± 18	< 0.001
MD Global Disease Activity VAS, 100 mm	26 ± 11	22 ± 10	< 0.001
ESR mm/h	30 ± 23	24 ± 18	0.02

NAN: North American Native; mHAQ: modified health assessment questionnaire; VAS: visual analog scale; ESR: erythrocyte sedimentation rate.

vs 0.47 in whites, p = nonsignificant), but the mHAQ score at the last clinic visit for these patients was significantly higher in NAN patients (0.90 vs 0.67, p = 0.002). Differences were greatest for those in Cohort 2, where both the mean and the last visit mHAQ scores were higher in NAN patients (0.72 vs 0.56, and 1.19 vs 0.86, respectively, both p < 0.001). For patients in Cohort 3, mean mHAQ scores were similar, but last-visit mHAQ scores were again higher in NAN patients (1.21 vs 1.02, p = 0.003).

Mean tender and swollen joint counts were similar between NAN and white patients (Figure 1); however, the Lansbury score was significantly higher in NAN patients for all 3 cohorts (48 vs 33 in white patients in Cohort 1; 40 vs 32 in Cohort 2; and 44 vs 35 in Cohort 3; p < 0.001 for all 3). This reflects the greater large joint involvement experienced by NAN patients with RA. Beginning in the early years of the disease, NAN patients are significantly more likely to have bilateral knee involvement (41% compared to 24% of whites, p = 0.016), with trends to greater shoulder and elbow involvement. Differences are most apparent in those in Cohort 2, with more frequent bilateral shoulder, elbow, and knee involvement in NAN patients: 59% vs 45%, p = 0.007; 53% vs 34%, p < 0.001; and 62% vs 48%, p = 0.007, respectively (Figure 2). Even among those in Cohort 3, with an average disease duration of 25 years, NAN patients had more frequent elbow and knee involvement: 64% vs 52% bilateral elbow involvement, p = 0.013; 71% vs 64% bilateral knee involvement, p = 0.003, in NAN versus white patients, respectively.

Treatment differences are also apparent. Treatment at the time of last clinical assessment is presented in Figure 3. Biologic treatment here includes only tumor necrosis factor (TNF-α) inhibitors, because rituximab and abatacept were not readily available at the time of data collection. "Other" disease-modifying antirheumatic drugs (DMARD) include cyclosporine, oral and parenteral gold, penicillamine, and minocycline. Use of methotrexate (MTX), biologics, leflunomide, and other DMARD did not differ significantly for the 2 groups. But NAN patients in cohorts 2 and 3 (those patients with greater than 5 years of disease duration) were more likely than whites to be treated with hydroxychloroquine (40% vs 25% in Cohort 2, p = 0.002; 26% vs 17% in Cohort 3, p = 0.005) and sulfasalazine (21% vs 12% in Cohort 2, p = 0.012; 20% vs 9% in Cohort 3, p < 0.001). Analyses of treatment differences over the entire disease course showed very similar results (data not shown), and are reflected by the greater mean number of DMARD (including biologics) taken by NAN patients in Cohorts 2 and 3 during their disease course: 3.4 DMARD compared to 2.7 in whites in Cohort 2 (p = 0.002); and 3.5 DMARD in NAN patients in Cohort 3 compared to 2.9 in whites, (p = 0.011; Table 3). NAN patients in Cohort 2 were also more likely to

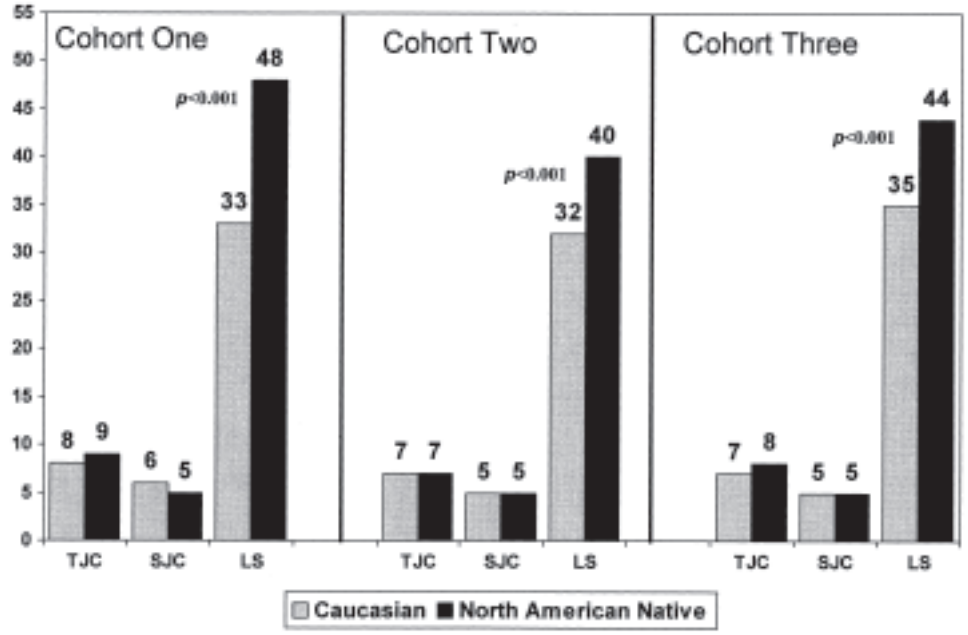

Figure 1. Mean joint counts in North American Native and white patients with rheumatoid arthritis. Cohort One: disease duration ≤ 5 years; Cohort Two: disease duration > 5 years, < 15 years; Cohort Three: disease duration > 15 years. TJC: tender joint count; SJC: swollen joint count; LS: Lansbury score.

be receiving combination DMARD therapy at their last clinic visit compared to whites (57% vs 44%, p = 0.026). Combination therapy did not differ in those with early (Cohort 1) or very late (Cohort 3) disease, but in all 3 cohorts, NAN patients were significantly more likely to be receiving prednisone at their last clinical assessment: 54% vs 35% in Cohort 1 (p = 0.013); 67% vs 46% in Cohort 2 (p < 0.001); and 74% vs 39% in Cohort 3 (p < 0.001; Table 3).

DISCUSSION

The data from our study describe a phenotype of severe, early onset, seropositive RA in NAN patients in central Canada, compared to whites being followed at the same center. More frequent seropositivity for RF and ANA, higher RF titer, higher ESR, greater large joint involvement, higher physician-reported and patient-reported disease activity, and higher mHAQ scores are apparent in the early years of disease, become most evident in those with moderate disease duration, and are still noticeable, although perhaps less so, in patients with very longstanding disease. This is in the setting of treatment that appears more aggressive, with greater numbers of DMARD used, more frequent combination therapy, and more frequent use of corticosteroids. However, it is not clear whether these differences are due to biological factors, inadequate treatment, or additional as yet unknown factors.

The pattern of greater large joint involvement, particularly elbow and knee involvement, has not been described. In addition to higher Lansbury scores, it is likely that this pattern also contributes to the higher mHAQ scores reported by NAN patients. Again, it is not clear whether this is part of a biologic phenotype or relates to treatment differences or other factors.

The earlier onset of RA in NAN patients described here has been observed in other NAN populations as well[2,3,16,22,23]. The implications of early disease onset, in addition to contributing to increased prevalence rates, include increased lifetime accumulation of deformity, disability, and drug toxicity, and perhaps higher premature mortality rates.

The high proportion of NAN patients positive for RF and ANA is perhaps indicative of biologic severity. RF, particularly at high titer, and ANA are generally considered to be poor prognostic markers in RA[12,13,24]. Several other populations of NAN patients with RA have also reported a frequency of RF > 90%, including the Yakima, Tlingit, Chippewa, Mazahua, Kiowa, and Oklahoma Indian patients, compared to the generally reported RF frequency of 75%–80% in patients with RA[3,8,16,17,22,25,26]. Similarly, the frequency of positive ANA in patients with RA was found to be higher than expected in these same NAN populations with RA, at 34%–75%. While we do not have anti-cyclic citrullinated peptide (anti-CCP) data for these cohorts, a subset of 266 of these same patients, participating in another study at our center, were found to be 82% anti-CCP-positive[27]. This population is also known to have a very high prevalence of the shared epitope: in El-Gabalawy, *et al*, 75% of patients with RA and unaffected controls were found to have the shared epitope[27], and in another study of juvenile RA in NAN children, 63% of RA

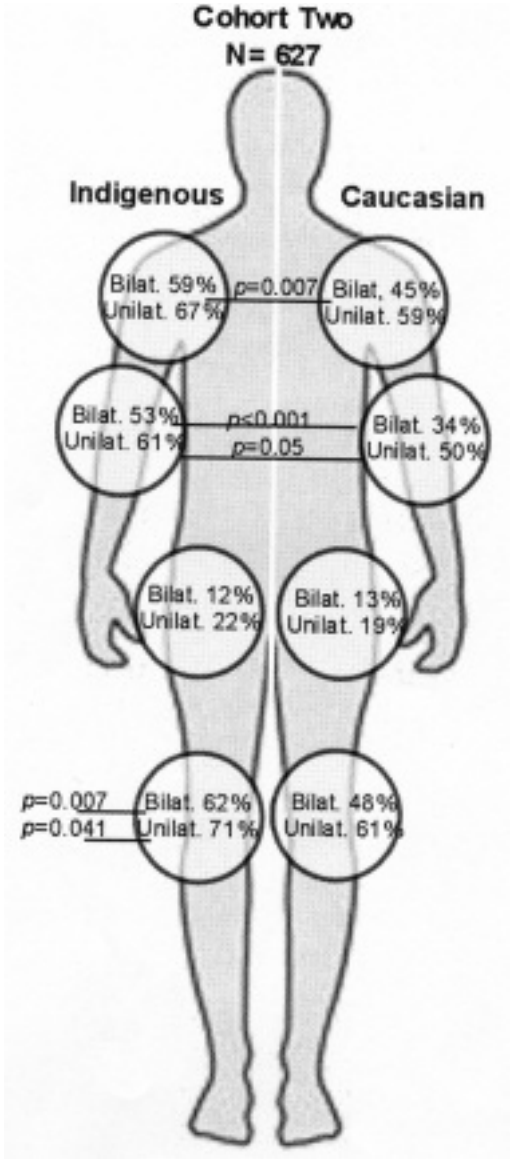

Figure 2. Large joint involvement in North American Native and white patients with rheumatoid arthritis, Cohort Two, disease duration > 5 years, < 15 years.

patients and 59% of controls had the shared epitope[28]. These serologic differences may suggest greater biologic severity or susceptibility.

Cigarette smoking may also play a role in this population. Reported smoking rates for Canadian NAN adults are high, at 59%, more than twice the rate of 24% for non-NAN Canadian adults[29,30]. While cigarette smoking has been unambiguously shown to increase the risk of developing RA[31,32], it is also clear that smoking acts in combination with genetic and other environmental risk factors. A large Swedish epidemiologic study suggested that smoking is strongly associated with anti-CCP-positive RA, and our study among others suggests a gene-environment interaction between smoking and shared epitope alleles[33,34,35]. More recently, a lesser response to both MTX and TNF-α inhibitors was also demonstrated in smokers compared to nonsmokers[36].

Other factors may also play a role. Many NAN patients live in remote locations, up to 1000 km or more from our specialist clinics, making followup and monitoring for treatment efficacy and safety difficult. We have shown that, in spite of indicators of severe disease, NAN patients have less frequent followup visits to our clinic compared to whites[37]. While physician visits and hospitalizations are covered for all Manitobans under the same universal, publicly funded healthcare system, NAN Manitobans are also funded for travel to medical appointments through a federal program. In spite of this, an analysis of healthcare use by Manitoba NAN people showed overall reduced contact with specialists for NAN compared to other Manitobans, unrelated to either geography or health indicators[38,39].

It is probable that differences in insurance coverage for medications also play a role. Treaty-status NAN Manitobans have coverage for medications through a federally funded program, while all other Manitobans are covered through a provincially funded plan. The federally funded plan for NAN people has stricter guidelines and requires more drug failures to access medications such as leflunomide, cyclosporine, and TNF-α inhibitors. It is likely that this accounts for some of the higher frequency of sulfasalazine and hydroxychloroquine use observed in NAN patients, as well as the similar rates of biologic use in spite of more severe disease.

There are some limitations to our study. First, we do not have radiologic data, and therefore cannot comment on joint damage. More importantly, our database does not contain information on the interval between disease onset and initiation of treatment. While date of onset of disease is recorded at the first visit regardless of the stage of a patient's disease, treatment received prior to attending our center is not reliably recorded. Therefore patients may have had treatment initiated by primary care physicians or other rheumatologists prior to being seen at our center; shortages of rheumatologists over the years also resulted in delayed referrals and treatment initiation. Although prior studies in Manitoba have documented a high rate of general physician visits for arthritis in NAN people[37], underreferral to specialists in general compared to non-NAN people has also been reported, in spite of worse health indicators[38,39]. Therefore it is possible that the worse outcome in NAN patients may be due in part to delayed treatment, or a missed "window of opportunity." The difference in disease severity is not likely to be due to disproportionate referral rates of severe patients to our center. Our hospital functions as a tertiary referral site for both NAN and all other Manitobans. In addition, all rheumatologists in the province practice in our city, and over the years of the study, the majority have been located at our hospital site.

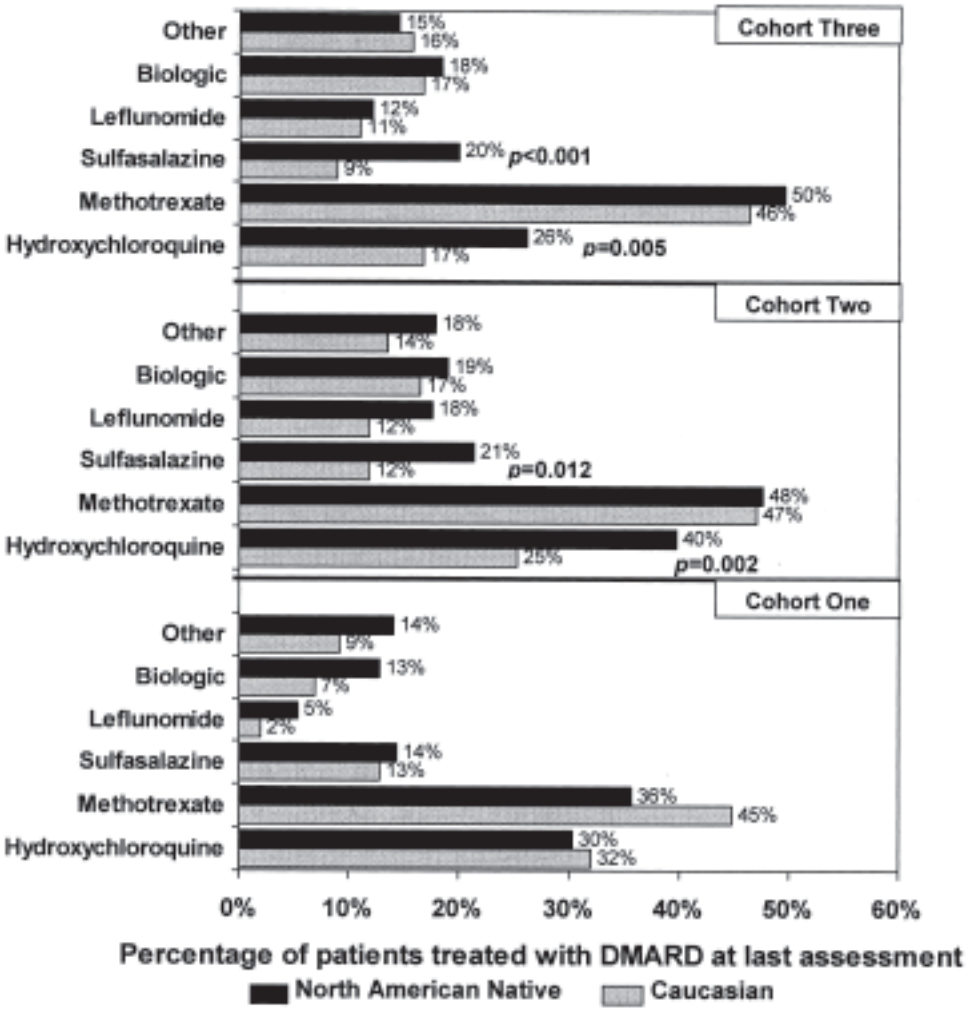

Figure 3. Disease-modifying antirheumatic drug (DMARD) treatment at time of last clinical assessment. Cohort One: disease duration ≤ 5 years; Cohort Two: disease duration > 5 years, < 15 years; Cohort Three: disease duration > 15 years. "Other" treatment includes cyclosporine, oral and parenteral gold treatment, penicillamine, and minocycline. Percentages add up to > 100 because patients may be taking more than 1 DMARD concomitantly.

Table 3. Treatment differences. Patient total n = 1796.

Type of Treatment	NAN, n = 481	White, n = 1315	p
Prednisone treatment at last visit, %			
Cohort 1, n = 348	54	35	0.013
Cohort 2, n = 647	67	46	< 0.001
Cohort 3, n = 801	74	39	< 0.001
Combination treatment at last visit, %			
Cohort 1, n = 348	41	36	NS
Cohort 2, n = 647	57	44	0.026
Cohort 3, n = 801	48	39	NS
Number of DMARD (ever), mean number ± SD			
Cohort 1, n = 348	1.9 ± 1.4	1.6 ± 1.5	NS
Cohort 2, n = 647	3.4 ± 2.0	2.7 ± 2.2	0.002
Cohort 3, n = 801	3.5 ± 2.3	2.9 ± 2.6	0.011

NAN: North American Native; DMARD: disease-modifying antirheumatic drug.

While our study documents aggressive disease with worse outcomes in NAN patients with RA, which has long been suspected by those caring for them, it raises many questions. There is an urgent need to further define those factors that may be contributing to poor outcomes in NAN patients with RA, in order to develop more timely and appropriate interventions for this rapidly growing segment of the Canadian population.

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