RHEUMATOLOGY

Rheumatology 2020;59:1725–1733
doi:10.1093/rheumatology/kez622
Advance Access publication 21 January 2020

Original article

Clinical characteristics and comorbidities in adult-onset Still's disease using a large US administrative claims database

Aleksander Lenert [1], GYeon Oh[2], Michael J. Ombrello[3] and Sujin Kim[4]

Abstract

Objectives. We aimed to describe clinical characteristics, treatment patterns and major comorbidities of a US-based adult-onset Still's disease (AOSD) cohort.

Methods. Administrative claims data from Truven MarketScan were collected from 2009 to 2015. An AOSD case was defined as ≥1 M06.1 International Classification of Diseases 10th revision (ICD-10) medical claim code. We extracted data for the AOSD cohort ($n = 106$) and 1:5 matched controls ($n = 530$) without AOSD. Outcomes of interest and a novel claims-based set of Yamaguchi criteria were identified by relevant ICD 9th revision (ICD-9) and ICD-10 codes. Bivariate descriptive analyses were conducted on all variables. Comorbidity rates and rate ratios were calculated in AOSD cases and matched controls. Statistical significance of cohort differences was determined to compare AOSD cases and matched controls.

Results. The AOSD cohort, with a mean age of 43.08 (standard deviation, SD. 13.9) years and with female predominance (68.9%) was observed over a mean of 750.12 (637.6) days. A total of 35.9% of AOSD patients fulfilled claims-based Yamaguchi criteria compared with 0.4% matched controls ($P < 0.05$). We identified severe AOSD-related complications, including macrophage activation syndrome (4.7%) and acute respiratory distress syndrome (12.3%). Treatment commonly involved systemic glucocorticoids (62.2%), MTX (51%) and anakinra (24.5%). Compared with matched controls, serious infections were significantly increased (rate ratio 2.58, 95% CI: 1.53, 4.37, $P = 0.0004$), while hyperlipidaemia (0.54, 95% CI: 0.35, 0.85; $P = 0.008$) and obesity (0.30, 95% CI: 0.15, 0.62; $P = 0.001$) were significantly decreased in AOSD patients.

Conclusion. We characterized a first US-based AOSD cohort using a large national administrative claims database, and identified key complications, treatments and comorbidities.

Key words: Adult-onset Still's disease, administrative claims data, outcomes research, comorbidities

CLINICAL SCIENCE

Rheumatology key messages

- Serious complications, such as macrophage activation syndrome (MAS) and pulmonary disease, were identified in the adult-onset Still's disease (AOSD) cohort.
- The most commonly observed treatment strategies for AOSD include systemic steroids, methotrexate and anakinra.
- Infection risk is higher in AOSD patients compared with matched controls.

Introduction

Adult-onset Still's disease (AOSD) is an autoinflammatory syndrome driven by the innate immune system. AOSD is triggered by activation of the inflammasome and subsequent systemic release of pro-inflammatory cytokines, such as IL-1, leading to the clinical manifestations of fever, rash, arthritis, pharyngitis, hepatitis and

[1]Division of Rheumatology, Department of Internal Medicine, University of Kentucky, [2]Department of Epidemiology, Kentucky Injury Prevention and Research Center, University of Kentucky College of Public Health, Lexington, KY, [3]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD and [4]Division of Biomedical Informatics, University of Kentucky College of Medicine, Lexington, KY, USA

Submitted 28 May 2019; accepted 7 November 2019

Correspondence to: Aleksander Lenert, Division of Immunology, Department of Internal Medicine, Carver College of Medicine, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242.
E-mail: aleksander-lenert@uiowa.edu.

accompanying constitutional symptoms [1]. Systemic glucocorticoids represent the backbone of therapy, to which synthetic and biological disease-modifying anti-rheumatic drugs (DMARDs) are sequentially added for induction of remission and steroid-sparing effect [2–4]. Novel treatments with IL-1 receptor antagonists and IL-6 inhibitors have been promising for symptom control in AOSD patients [3]. However, due to its rarity and paucity of longitudinal cohorts, long-term outcomes in AOSD remain unknown [2].

An increased comorbidity burden has been well established for more common rheumatic diseases, including RA and SLE [5–8]. The increased risk of comorbid conditions has implications for screening and prevention to improve long-term health in patients with rheumatic diseases. Current epidemiologic studies in AOSD, all conducted outside of North America, focus on disease-related features and complications, but do not address comorbidities in this at-risk population [2, 9–14]. Hence, to address this gap, we sought to characterize major comorbidities in AOSD patients. The aims of our study were to identify an AOSD cohort utilizing a large US administrative database, describe the clinical characteristics and treatments of the AOSD cohort, and identify comorbidities of the AOSD cohort compared with matched controls from the background population.

Methods

Data source

We conducted an observational cohort study of previously collected administrative claims data utilizing Truven Health Analytics MarketScan Commercial Claims and Encounters database, from 1 January 2009 to 30 December 2015. This large US national database contains de-identified information of employer-sponsored private health insurance claims for patients aged <65 years. The MarketScan database includes complete longitudinal records of inpatient and outpatient services, and prescription drug claims, with associated billing codes from the International Classification of Diseases, ninth and tenth revisions, Clinical Modification (ICD-9-CM and ICD-10-CM), Current Procedural Terminology (CPT) codes and National Drug Codes (NDC). Race, geographic data, inpatient medication usage, laboratory study results and information regarding death are not available in the database. During 2009–2015, MarketScan included data from >90 million individual patients. The University of Kentucky's Institutional Review Board (IRB) has approved the use of de-identified claims data from MarketScan for research purposes; hence, individual IRB approval for this study was not required.

Patient selection

AOSD cases were defined as patients with medical claims with ≥1 diagnostic code for AOSD (ICD-10-CM code M06.1) in any claim field from 1 January 2009 to 30 December 2015 [13]. To improve accuracy of AOSD case identification, we also examined diagnostic codes for systemic arthritis (ICD-9-CM codes 714, 714.2 or 714.3), which present at onset in at least 75% of AOSD cases. The index date was defined as the date of the first AOSD diagnosis (either ICD-9-CM codes 714, 714.2 or 714.3, or ICD-10-CM M06.1). In addition to fulfilling ≥1 M06.1 code, 98/106 AOSD cases had ≥1 of the ICD-9-CM codes for systemic arthritis. We included only AOSD cases who were ≥18 years of age at index date and had continuous eligibility for ≥180 days prior to the index date (i.e. baseline period). Patients were excluded if they had any of the following: gap of enrolment >1 month; claim for another rheumatic disease (i.e. RA, SLE, psoriatic arthritis, granulomatosis with polyangiitis, giant cell arteritis); or claim for another autoinflammatory syndrome (i.e. FMF, Behçet's disease and cryopyrin associated periodic syndromes). Patients with AOSD were matched to control patients without AOSD from the same population in MarketScan at a ratio of 5:1 based on age, sex and index date (month and year). These matched controls had the same inclusion requirements as AOSD cases, except for the diagnosis of AOSD. All patients in the cohort had a variable length of follow-up until the earliest occurrence of: outcome of interest, end of continuous enrolment or end of the study period (30 December 2015).

Study variables and definitions

All patient demographic data, including age, sex, duration of follow-up and comorbidity index were collected from the record at the time of the index AOSD coding. We calculated the Charlson Comorbidity Index (CCI) for both AOSD cases and controls during the pre-index period as previously reported [15]. Outcomes, complications and comorbidities were analysed from the entire AOSD cohort during the study period (post-index to end of study). Outcomes of interest were defined using diagnostic codes (ICD-9-CM and ICD-10-CM) or standard algorithms for outpatient data [7, 8, 16]. The ICD-9-CM and ICD-10-CM codes used for these conditions are available upon request from the authors.

Comorbidities were identified using diagnostic codes in medical claims; however, claims for non-diagnostic or rule-out procedures (i.e. laboratory, pathology, radiology services) were excluded to avoid incorrectly identifying patients as having a comorbidity. We counted only the first occurrence of the diagnostic code of a given comorbidity after the index date of AOSD cases and the corresponding index date in the comparison cohort [8]. For infections, we describe total infections and serious infections defined as those requiring hospitalization [16]. Cardiovascular disease events were a composite group identified by any ICD code for ischaemic heart disease, myocardial infarction and/or stroke. Pharmacy prescriptions were identified by NDC codes. We grouped medications into major AOSD treatment categories: NSAIDs, systemic glucocorticoids, non-biological (nbDMARD) and biological DMARDs (bDMARD).

Additionally, we introduce and analyse an adapted version of the Yamaguchi criteria for claims-based research, by identifying ICD-9-CM/ICD-10-CM codes reflective of the major and minor Yamaguchi criteria [1]. We included all Yamaguchi criteria defined by claims codes, except for the criterion of 'negative tests for antinuclear antibody (IF) and rheumatoid factor (IgM)' as this information is not captured in the MarketScan database (Supplementary Table 1, available at *Rheumatology* online). We identified the proportion of the AOSD cohort who meet the proposed claims-based Yamaguchi diagnostic criteria, defined as meeting a total of $\geq$4 criteria and $\geq$2 major criteria by ICD codes observed from baseline to end of study.

Statistical analysis

Bivariate descriptive analyses were conducted on all study variables comparing patients with AOSD and matched controls. Categorical variables were expressed as counts and percentages. Continuous data were summarized with means and standard deviations, or medians and interquartile ranges as appropriate.

We calculated the comorbidity rate by dividing the number of cases or controls being diagnosed with the comorbidity of interest by the sum of person-time during the follow-up period. The person-time was defined as the number of days each person was followed from the date of the diagnosis for AOSD or index date for controls until the earliest of the following: date for the diagnostic code of outcome of interest in medical claims, disenrollment date, or end of study (30 December 2015). The comorbidity ratio was calculated by dividing the comorbidity rate for AOSD cases by the corresponding rate for the controls. A rate ratio of $>$1 indicates a higher comorbidity rate in AOSD cases than controls. Conversely, a rate ratio of $<$1 indicates a lower comorbidity rate in AOSD cases than controls [8].

When appropriate, the statistical significance of cohort differences in bivariate descriptive statistics used χ^2 for categorical variables and t-tests for differences in continuous variables for normally distributed variables. Nonparametric testing, i.e. Wilcoxon rank sum test, was used for analysis of skewed continuous variables [17]. The threshold for statistical significance was set a priori at a *P*-value of 0.05.

Results

We identified a cohort of 106 AOSD patients for inclusion in our study. The baseline characteristics of our study participants are shown in Table 1. The mean age (S.D.) of the AOSD cohort was 43.08 (13.9) with a female predominance (68.9%). The mean follow-up time (S.D.) was 750.12 (637.6) days in the AOSD cohort. A total of 530 control subjects were sampled and matched according to the study criteria. The mean CCI was significantly higher for the AOSD cohort compared with controls ($P < 0.0001$).

Clinical characteristics of AOSD

At baseline, the cardinal clinical manifestations of AOSD were commonly identified by medical claims codes, including fever (49.1%), arthritis (45.3%), rash (29.3%), leucocytosis (23.6%), pharyngitis (20.8%), hepatic dysfunction (10.4%), lymphadenopathy (13.2%) and hepatomegaly or splenomegaly (6.6%).

During the study period, serosal involvement was very commonly observed in AOSD patients (17% pleural and 10.4% pericardial involvement). Anaemia was present in 27.4% of AOSD patients. The majority of AOSD patients underwent laboratory testing for acute phase reactants and disease activity markers, including C-reactive protein (81.1%), erythrocyte sedimentation rate (80.2%) and serum ferritin (57.6%). Bone marrow biopsy was observed in 4.7%. Overall, in addition to meeting the study inclusion criteria, 35.9% of AOSD patients fulfilled the proposed claims-based Yamaguchi criteria compared with only 0.4% of matched controls ($P < 0.05$).

Severe complications of AOSD

During the study period, we observed several severe manifestations of AOSD in our cohort, including renal dysfunction (6.6%), pancytopenia (5.7%), macrophage activation syndrome (MAS, 4.7%), non-infectious meningitis (1.9%), myocarditis (1.9%) and disseminated intravascular coagulation (0.9%). In addition, pulmonary manifestations were commonly identified, including acute respiratory distress syndrome (ARDS, 12.3%) and interstitial lung disease (ILD, 1.9%).

Treatment in AOSD

Therapeutic strategies identified in the AOSD cohort are shown in Table 2. Systemic glucocorticoids and nbDMARDs were each prescribed in 62.2% of AOSD patients respectively, while NSAIDs were prescribed in only 27.6%. MTX (51%) and hydroxychloroquine (21.4%) were the most commonly prescribed nbDMARDs. The immunosuppressant group (i.e. azathioprine and ciclosporin) was the least commonly prescribed (8.2%). The IL-1 receptor antagonist anakinra was the most commonly prescribed biological DMARD (bDMARD) in 24.5% of AOSD patients, while the anti-TNF group was prescribed in 20.4%.

Comorbidity rates and rate ratios in AOSD compared with matched controls

Comorbidity rates

In the AOSD cohort, the highest absolute comorbidity rate (Table 3) was observed for infection [21.76/10 000 person-days (PD), 95% CI: 17.09, 27.33], followed by hypertension (HTN; 6.81/10 000 PD, 95% CI: 4.86, 9.29), hyperlipidaemia (HLD; 3.79/10 000 PD, 95% CI: 2.44, 5.65), cardiovascular events (CVD; 3.07/10 000

Table 1 Baseline characteristics of patients with AOSD and matched controls

	AOSD ($n = 106$)	Control ($n = 530$)	*P*-value
Age[a], mean (S.D.) years	43.08 (13.9)	43.08 (13.9)	NA[b]
Female, *n* (%)	73 (68.9)	365 (68.9)	NA[b]
Follow-up time, mean (S.D.) days	750.12 (637.6)	580.11 (536.19)	**0.01**
CCI, mean (S.D.)	1.33 (1.58)	0.81 (1.53)	**<0.0001**

An alpha level of 0.05 was used for all statistical tests. [a]Age represents an individual's age at index date. [b]Matched variable. AOSD: Adult-onset Still's disease; NA: not applicable; CCI: Charlson Comorbidity Index.

Table 2 Treatment characteristics of patients with AOSD

Treatment	AOSD ($n = 98$)[a]
Glucocorticoids, *n* (%)	61 (62.2)
NSAID, *n* (%)	27 (27.6)
nbDMARD, *n* (%)	61 (62.2)
Methotrexate	50 (51.0)
Hydroxychloroquine	21 (21.4)
Leflunomide	7 (7.1)
Sulfasalazine	4 (4.1)
IL-1/IL-1R antagonist	25 (25.5)
Anakinra	24 (24.5)
Canakinumab	1 (1.0)
Rilonacept	0 (0)
Anti-TNF	20 (20.4)
Adalimumab	9 (9.2)
Certolizumab	0 (0)
Etanercept	10 (10.2)
Golimumab	2 (2.0)
Infliximab	1 (1.0)
Immunosuppressant	8 (8.2)
Cyclosporine	3 (3.1)
Tacrolimus	0 (0)
Azathioprine	4 (4.1)
Mycophenolate	2 (2.0)

[a]98/106 patients with AOSD had prescription information available. nbDMARD: non-biological disease modifying anti-rheumatic drug.

PD, 95% CI: 1.93, 4.66) and malignancy (2.3/10 000 PD, 95% CI: 1.39, 3.61). In the comparison cohort, the highest comorbidity rates were observed for infection (22.48/10 000 PD, 95% CI: 20.06, 25.12), HTN (8.21/10 000 PD, 95% CI: 7.04, 9.51), HLD (6.98/10 000 PD, 95% CI: 5.92, 8.17), obesity (3.52/10 000 PD, 95% CI: 2.86, 4.30) and CVD events (2.25/10 000 PD, 95% CI: 1.74, 2.87). The rates of serious infections requiring hospitalization were 3.35/10 000 PD (95% CI: 2.15, 4.99) in the AOSD cohort and 1.30/10 000 PD (95% CI: 0.93, 1.76) in the comparison cohort.

The rate ratios

The rate ratios of comorbidities in AOSD are shown in Table 3. The highest rate ratio was observed for serious infections requiring hospitalization (2.58, 95% CI: 1.53, 4.37, $P = 0.0004$). Rate ratios for malignancy (1.59, 95% CI: 0.90, 2.79) and CVD (1.36, 95% CI: 0.82, 2.26) were >1, but did not reach statistical significance. The rate ratios for HLD (0.54, 95% CI: 0.35, 0.85, $P = 0.008$) and obesity (0.30, 95% CI: 0.15, 0.62, $P = 0.001$) were significantly lower in the AOSD cohort. Rate ratios for infection (0.97, 95% CI: 0.75, 1.25), HTN (0.83, 95% CI: 0.58, 1.18) and smoking (0.69, 95% CI: 0.33, 1.46) were <1, but did not reach statistical significance.

Sex-specific rates

The rates and rate ratios stratified by sex are shown in Table 4. The highest rate ratio for men with AOSD was observed for serious infections requiring hospitalization (4.30, 95% CI: 1.95, 9.46, $P = 0.0003$), while the lowest rate ratio was observed for HLD (0.45, 95% CI: 0.21, 0.99). The lowest rate ratio in women with AOSD was observed for obesity (0.37, 95% CI: 0.18, 0.78, $P = 0.008$).

Discussion

This study of 106 cases of AOSD is the first epidemiologic study to provide insight into the clinical features, complications and treatment of a large AOSD cohort in the United States. This study is also the first to identify and describe major comorbidities in an AOSD cohort compared with a matched reference cohort from the background population.

We demonstrate the utility of a large US administrative claims database to perform an observational cohort study of outcomes and comorbidities of a rare rheumatic disease [18]. Prospective longitudinal patient registries of rare rheumatic diseases such as AOSD are currently unavailable. In addition, prospective cohorts are time and resource intensive, collect only pre-specified outcomes and are not representative of routine clinical care [18]. Administrative claims data, such as Truven MarketScan, provide population-based information on millions of individual patients, including valid and reliable dispensation data on medications and comprehensive coding for important outcomes of interest. Observational and pharmacoepidemiologic studies utilizing administrative claims have been carried out successfully in RA, SLE and gout to advance our understanding of these common rheumatic diseases [19–22]. Recently, Sakata

Table 3 Rates and rate ratios of selected comorbidities among AOSD patients against reference population

Comorbidity	AOSD (n = 106)			Control (n = 530)				
	n	Person-days	Rate (95% CI)	n	Person-days	Rate (95% CI)	Rate Ratio (95% CI)	P
Infection	70	32 173	21.76 (17.09, 27.33)	304	135 219	22.48 (20.06, 25.12)	0.97 (0.75, 1.25)	0.80
Serious infection	22	65 726	3.35 (2.15, 4.99)	38	293 287	1.30 (0.93, 1.76)	2.58 (1.53, 4.37)	**0.0004**
Malignancy	17	73 900	2.3 (1.39, 3.61)	42	289 502	1.45 (1.06, 1.94)	1.59 (0.90, 2.79)	0.11
Cardiovascular event	20	65 184	3.07 (1.93, 4.66)	62	275 619	2.25 (1.74, 2.87)	1.36 (0.82, 2.26)	0.23
Hypertension	37	54 367	6.81 (4.86, 9.29)	171	208 390	8.21 (7.04, 9.51)	0.83 (0.58, 1.18)	0.30
Hyperlipidaemia	22	58 016	3.79 (2.44, 5.65)	149	213 576	6.98 (5.92, 8.17)	0.54 (0.35. 0.85)	**0.008**
Obesity	8	75 822	1.06 (0.49, 2.00)	92	261 233	3.52 (2.86, 4.30)	0.30 (0.15, 0.62)	**0.001**
Smoking	8	72 469	1.10 (0.51, 2.10)	46	287 016	1.60 (1.19, 2.12)	0.69 (0.33, 1.46)	0.33

Rates (per 10 000 days of follow-up) and rate ratios of selected comorbidities amongst 106 patients with AOSD and 530 age-, sex- and index date-matched controls from the reference population. An alpha level of 0.05 was used for all statistical tests. AOSD: Adult-onset Still's disease.

Table 4 Rates and rate ratios of selected comorbidities of AOSD patients against reference population by gender

	n	Person days	Rate (95% CI)	n	Person days	Rate (95% CI)		P
Infection								
Male	20	9737	20.54 (12.9, 31.16)	73	51 534	14.17 (11.18, 17.71)	1.45 (0.88, 2.38)	0.14
Female	50	22 436	22.29 (16.72, 29.14)	231	83 685	27.6 (24.21, 31.34)	0.81 (0.59, 1.10)	0.17
Serious infection								
Male	11	15 952	6.90 (3.63, 11.99)	14	87 206	1.61 (0.91, 2.63)	4.30 (1.95, 9.46)	**0.0003**
Female	11	49 774	2.21 (1.16, 3.84)	24	206 081	1.17 (0.76, 1.71)	1.90 (0.93, 3.87)	0.08
Malignancy								
Male	5	21 187	2.36 (0.86, 5.23)	14	87 004	1.61 (0.92, 2.64)	0.71 (0.45, 1.14)	0.16
Female	12	52 713	2.28 (1.23, 3.87)	28	202 498	1.38 (0.94, 1.97)	1.65 (0.84, 3.24)	0.15
Cardiovascular event								
Male	8	16 902	4.73 (2.20, 8.99)	26	79 068	3.29 (2.19, 4.75)	1.44 (0.65, 3.18)	0.37
Female	12	48 282	2.49 (1.35, 4.23)	36	196 551	1.83 (1.30, 2.51)	1.36 (0.71, 2.61)	0.36
Hypertension								
Male	16	13 674	1.17 (0.69, 1.86)	60	54 996	1.09 (0.84, 1.40)	1.07 (0.62, 1.86)	0.80
Female	21	40 693	5.16 (3.28, 7.75)	111	153 394	7.24 (5.98, 8.68)	0.71 (0.45, 1.14)	0.16
Hyperlipidaemia								
Male	7	17 018	4.11 (1.80, 8.14)	54	59 418	9.09 (6.90, 11.77)	0.45 (0.21, 0.99)	**0.05**
Female	15	40 998	3.66 (2.13, 5.90)	95	154 158	6.16 (5.01, 7.50)	0.59 (0.34, 1.02)	0.06
Obesity								
Male	0	23 408	—	20	84 683	2.36 (1.48, 3.58)	—	—
Female	8	52 414	1.53 (0.71, 2.90)	72	176 550	4.08 (3.21, 5.11)	0.37 (0.18, 0.78)	**0.008**
Smoking								
Male	3	21 001	1.43 (0.36, 3.89)	16	86 269	1.86 (1.10, 2.95)	0.77 (0.22, 2.64)	0.68
Female	5	51 468	9.72 (3.56, 21.53)	30	200 747	1.49 (1.03, 2.11)	0.65 (0.25, 1.68)	0.37

Rates (per 10 000 days of follow-up) and rate ratios of selected comorbidities amongst 73 women and 33 men with AOSD, compared with 365 women and 165 men age-, sex- and index date-matched controls from the reference population. An alpha level of 0.05 was used for all statistical tests.

et al. used a Japanese administrative database to characterize severe manifestations of hospitalized patients with AOSD [13]. Our study used a similar approach to identify an AOSD cohort with a specific ICD-10-CM code for AOSD (i.e. M06.1); however, it is important to note that the accuracy of M06.1 for the diagnosis of AOSD is unknown and to our knowledge there are no published reports on its accuracy in administrative or linked electronic medical record (EMR)-claims datasets.

Our study demonstrates that our AOSD cohort is similar in mean age and sex distribution to prior reported AOSD studies [2, 9–14]. The mean follow-up time of

>2 years in our AOSD cohort is slightly shorter than in other AOSD studies, likely due to the timeframe for data availability in Truven. The typical clinical features of AOSD were readily identifiable with coded data in our study, including the classic triad of fever, arthritis and rash characteristic of AOSD. Additionally, only one-third of AOSD patients fulfilled our proposed claims-based Yamaguchi criteria highlighting the limitation of claims data to capture all AOSD related manifestations. Due to variable coding practices across providers (i.e. rheumatologist compared with non-rheumatologist), clinical setting and institutions, the proportion of patients meeting claims-based Yamaguchi criteria is likely an underestimate; hence, they may be too stringent for claims-based research and will warrant modification if used in future claims-based comparative effectiveness studies.

We identified several major complications of AOSD, including MAS, disseminated intravascular coagulation, myocarditis and non-infectious meningitis. The prevalence of MAS in our cohort (∼4.7%) was slightly lower than previously reported [9–14, 17]. Our AOSD cohort predominantly received clinical care in the outpatient setting, in contrast to the recent study by Sakata *et al.* with an inpatient AOSD cohort [13]. MAS is a severe complication frequently occurring at initial onset of AOSD that requires aggressive immunosuppressive therapy to decrease mortality [23]. We also identified important pulmonary manifestations in the AOSD cohort, including ARDS in 12% and ILD in 2%. Parenchymal lung involvement (PLI) was found to occur in 5.3% of AOSD patients in a French cohort, with ARDS being the most common and severe manifestation [24]. AOSD-related ILD occurred in 11.5% of AOSD patients in a Japanese cohort and was associated with a significantly higher rate of MAS and relapses [25]. Similarly, severe and often fatal pulmonary manifestations have been identified in systemic juvenile idiopathic arthritis (SJIA), including pulmonary arterial hypertension, ILD and alveolar proteinosis [26]. Further characterization of pulmonary manifestations is needed to guide treatment decisions and long-term follow-up of these severe complications in AOSD.

By analysing medication prescription and dispensation data, we were able to describe general therapeutic strategies in patients with AOSD in the USA ∼ two-thirds of the AOSD cohort received systemic steroids and/or traditional nbDMARDs, most commonly MTX. This treatment approach is consistent with the initial strategies employed for the management of systemic and articular manifestations of AOSD [3]. Moreover, bDMARDs are commonly prescribed for persistently active or refractory AOSD manifestations. In our AOSD cohort, ∼25% of patients received treatment targeting the IL-1 inflammatory axis, and an additional ∼20% of received anti-TNF therapy. Given the timeframe of our cohort study (2009–2015) in relation to the timing of IL-1/IL-1 receptor (IL-1R) targeted drug approvals in the USA, all except one patient with AOSD received anakinra. This proportion of IL-1/IL-1R blocker use is higher in our AOSD cohort in comparison to non-US studies, mainly given the availability of anakinra in the USA since 2003 for the management of RA. Anti-TNF treatment was the second most commonly prescribed bDMARD group, likely due to TNF's suspected role in the pathogenesis of AOSD. Additionally, anti-TNF's efficacy and favourable side-effect profile are well-established in clinical practice in the USA for RA and psoriatic arthritis. Of note, neither anakinra nor anti-TNFs have received US Food and Drug Administration (FDA) approval for the treatment of AOSD in the USA. Surprisingly, we did not identify any AOSD patients on IL-6 antagonists, despite tocilizumab's availability in the USA since 2010, its FDA indication for the management of SJIA and its reported efficacy for refractory AOSD [27–29]. Additional future therapies for AOSD include targeted therapy against IL-18, a potent pro-inflammatory cytokine and disease activity marker in AOSD, which will need to be studied in early phase clinical trials [29–31].

Our study is the first to describe selected major comorbidities in an AOSD cohort compared with matched controls from the same population. At baseline, the mean CCI score was significantly higher in AOSD patients compared with controls (Table 1). The CCI is a validated predictive index that accounts for multiple morbidities present in each subject (categorized by ICD code) [15, 32]. A higher CCI score is associated with increased mortality and higher healthcare resource utilization. The list of comorbidities in the CCI includes coronary artery disease, diabetes mellitus and malignancy amongst others; of note, the CCI does not score for infectious outcomes [32].

Serious infections were 2.6 times more common in AOSD patients compared with controls, likely attributable to the use of systemic steroids and DMARDs for AOSD treatment. Of note, we did not adjust for steroid and/or DMARD use in the analysis. The finding of higher infection rate was significantly increased in men compared with women and will require additional research to understand sex-differences in infection rates in AOSD, after adjusting for medication use. It is important to note, however, that the initial clinical presentation and flares of AOSD frequently mimic infections. Hence, providers may mistakenly code for an infectious diagnosis instead of an AOSD-related manifestation, thus leading to an overestimate in the rate of infectious outcomes. We are unable to verify the reference standard for each infectious ICD code given the limitations inherent to claims databases such as Truven. A rate ratio >1 for malignancy suggests that AOSD may be associated with increased rate of malignancy; however, a longer observation period is needed to accurately assess this relationship due to the long latency period to a cancer diagnosis. In addition, further analysis of cancer subtypes may provide additional insight.

Despite the shared pro-inflammatory IL-1 axis of cardiovascular disease and AOSD, we did not find significantly increased CVD events in our AOSD cohort compared with matched controls [33–35]. In addition,

two important traditional CVD risk factors, hyperlipidaemia and obesity, were found to be significantly lower in the AOSD cohort compared with controls. We postulate that hyperlipidemia and obesity are less likely to be coded by providers in AOSD cases compared with controls due to their lower clinical priority and billing level incentives in the USA. It is also plausible that adequate immunosuppression with systemic steroids and anti-cytokine therapy lowers lipids in AOSD patients. Given the relative conservative size of our AOSD cohort, low CVD event rate and finding of CVD rate ratio >1, further studies into the postulated link between AOSD and CVD are needed. A longer duration of observation in a larger cohort of AOSD patients with a higher observed event rate would be needed to more accurately elucidate this relationship.

Limitations

Our study had some limitations inherent to any study with administrative claims data for observational research. First, the deidentified and unlinked structure of the Truven database precluded direct medical chart review of each individual's clinical and laboratory data to confirm case-control status and comorbidities; hence, the possibility of misclassification of AOSD cases and outcomes remains. The accuracy of the ICD-10 code M06.1 for the diagnosis of AOSD is unknown and to our knowledge there are no published reports on its accuracy in administrative or linked EMR-claims datasets. Based on our experience, the code M06.1 had excellent performance characteristics and accuracy for the diagnosis of AOSD (specificity 0.99, positive predictive value 0.92, and area under the receiver operator curve of 0.73) in a large tertiary care EMR with >1 million unique patients (A. Lenert, *submitted for publication*). However, our preliminary single institution findings have limited generalizability and future external validation is needed. Future studies of administrative claims linked to EMR data will be needed to determine the accuracy of ICD code-based diagnosis for AOSD. Utilization of EMR structured data, such as laboratory values and/or procedural codes, could help refine an AOSD cohort and characterize the disease course including flare rates and disease activity status.

Second, for inclusion into our cohort, an AOSD case required the presence of ≥ 1 specific code for AOSD (i.e. M06.1) as previously used in claims-based research [13]. In addition, 98 out of 106 AOSD cases had ≥ 1 code representative of systemic arthritis symptoms of AOSD, which we used to increase case validity. We also excluded potentially confounding diagnoses, such as FMF and other autoinflammatory syndromes. We recognize that our strict ASOD case definition likely led to a significant reduction in the size of the final AOSD cohort (estimated prevalence of $\sim$0.116 AOSD cases per 100 000 persons in Truven) of $\sim$9–10-fold compared with the expected prevalence of AOSD in the general population. In addition, the time period available for our study (2009–2015) likely contributed to fewer AOSD cases identified by M06.1, which was introduced during ICD-10 in 2015 in the USA. Access to additional follow-up years after 2015 in Truven and other US-based claims datasets would likely lead to a larger AOSD cohort for future research.

Third, coding of outcomes (for clinical characteristics and comorbidities) in claims databases can be highly variable and dependent on individual providers' coding practices. Thus, certain outcomes may not be captured in the Truven database. Hence, we suspect that our reported rates of outcomes are likely underestimates of true events occurring in this population. We acknowledge the limitations of claims data to fully capture the clinical manifestations and severe complications of AOSD longitudinally given the low prevalence of outcomes observed in our study. In addition, EMR phenotyping using natural language processing could be applied to unstructured data for validation of outcomes of interest in AOSD [36, 37].

Fourth, the mean observation period from the initial AOSD diagnosis until end of data availability may be short and hence may not capture long-term outcomes of interest such as malignancy and CVD events, which have a long latency to diagnosis. Finally, our results are applicable mainly to patients with private health insurance as represented in Truven, and have limited generalizability to the entire US population, which includes individuals with non-private health insurance (i.e. Medicaid or Medicare) and the uninsured.

Conclusion

In this observational cohort study, we utilized a large national administrative claims database to describe key clinical characteristics, complications and immunosuppressive treatment patterns of this first US-based AOSD cohort. We used claims data from all regions of the USA, including both inpatient and outpatient settings, to characterize the full continuum of care of an AOSD cohort. We identified key comorbidities in the AOSD, highlighting the increased the rate of serious infections especially in men with AOSD. Further studies in a larger cohort of AOSD patients will be needed to elucidate the proposed relationship between AOSD and cardiovascular disease.

Funding: The work was supported by the National Center for Advancing Translational Sciences at the National Institutes of Health [UL1TR001998]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Yamaguchi M, Ohta A, Tsunematsu T *et al*. Preliminary criteria for classification of adult Still's disease. J Rheumatol 1992;19:424–30.

2 Gerfaud-Valentin M, Maucort-Boulch D, Hot A *et al*. Adult-onset still disease: manifestations, treatment, outcome, and prognostic factors in 57 patients. Medicine 2014;93:91–9.

3 Govoni M, Bortoluzzi A, Rossi D, Modena V. How I treat patients with adult onset Still's disease in clinical practice. Autoimmun Rev 2017;16:1016–23.

4 Jamilloux Y, Gerfaud-Valentin M, Henry T, Seve P. Treatment of adult-onset Still's disease: a review. Ther Clin Risk Manag 2015;11:33–43.

5 Liao KP, Solomon DH. Traditional cardiovascular risk factors, inflammation and cardiovascular risk in rheumatoid arthritis. Rheumatology 2013;52:45–52.

6 Sousa S, Goncalves MJ, Ines LS *et al*. Clinical features and long-term outcomes of systemic lupus erythematosus: comparative data of childhood, adult and late-onset disease in a national register. Rheumatol Int 2016;36:955–60.

7 Walsh JA, Song X, Kim G, Park Y. Evaluation of the comorbidity burden in patients with ankylosing spondylitis using a large US administrative claims data set. Clin Rheumatol 2018;37:1869–78.

8 Englund M, Merkel PA, Tomasson G, Segelmark M, Mohammad AJ. Comorbidities in Patients with antineutrophil cytoplasmic antibody-associated vasculitis versus the general population. J Rheumatol 2016;43:1553–8.

9 Asanuma YF, Mimura T, Tsuboi H *et al*. Nationwide epidemiological survey of 169 patients with adult Still's disease in Japan. Mod Rheumatol 2015;25:393–400.

10 Kim YJ, Koo BS, Kim YG, Lee CK, Yoo B. Clinical features and prognosis in 82 patients with adult-onset Still's disease. Clin Exp Rheumatol 2014;32:28–33.

11 Liu Z, Lv X, Tang G. Clinical features and prognosis of adult-onset Still's disease: 75 cases from China. Int J Clin Exp Med 2015;8:16634–9.

12 Ruscitti P, Cipriani P, Masedu F *et al*. Adult-onset Still's disease: evaluation of prognostic tools and validation of the systemic score by analysis of 100 cases from three centers. BMC Med 2016;14:194.

13 Sakata N, Shimizu S, Hirano F, Fushimi K. Epidemiological study of adult-onset Still's disease using a Japanese administrative database. Rheumatol Int 2016;36:1399–405.

14 Sfriso P, Priori R, Valesini G *et al*. Adult-onset Still's disease: an Italian multicentre retrospective observational study of manifestations and treatments in 245 patients. Clin Rheumatol 2016;35:1683–9.

15 Quan H, Sundararajan V, Halfon P *et al*. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130–9.

16 Panupattanapong S, Stwalley DL, White AJ *et al*. Epidemiology and outcomes of granulomatosis with polyangiitis in pediatric and working-age adult populations in the United States: analysis of a large national claims database. Arthritis Rheumatol 2018;70:2067–76.

17 Ho KM, Finn J, Knuiman M, Webb SA. Combining multiple comorbidities with Acute Physiology Score to predict hospital mortality of critically ill patients: a linked data cohort study. Anaesthesia 2007;62:1095–100.

18 Desai RJ, Solomon DH. Use of large healthcare databases for rheumatology clinical research. Curr Opin Rheumatol 2017;29:138–43.

19 Kim SC, Solomon DH, Rogers JR *et al*. Cardiovascular safety of tocilizumab versus tumor necrosis factor inhibitors in patients with rheumatoid arthritis: a multi-database cohort study. Arthritis Rheumatol 2017;69:1154–64.

20 Barbhaiya M, Feldman CH, Guan H *et al*. Race/ethnicity and cardiovascular events among patients with systemic lupus erythematosus. Arthritis Rheumatol 2017;69:1823–31.

21 Feldman CH, Liu J, Feldman S, Solomon DH, Kim SC. Risk of high-grade cervical dysplasia and cervical cancer in women with systemic lupus erythematosus receiving immunosuppressive drugs. Lupus 2017;26:682–9.

22 Kim SC, Neogi T, Kang EH *et al*. Cardiovascular risks of probenecid versus allopurinol in older patients with gout. J Am Coll Cardiol 2018;71:994–1004.

23 Lenert A, Yao Q. Macrophage activation syndrome complicating adult onset Still's disease: a single center case series and comparison with literature. Semin Arthritis Rheum 2016;45:711–6.

24 Gerfaud-Valentin M, Cottin V, Jamilloux Y *et al*. Parenchymal lung involvement in adult-onset Still disease: a STROBE-compliant case series and literature review. Medicine 2016;95:e4258.

25 Takakuwa Y, Hanaoka H, Kiyokawa T *et al*. Adult-onset Still's disease-associated interstitial lung disease represents severe phenotype of the disease with higher rate of haemophagocytic syndrome and relapse. Clin Exp Rheumatol 2019;37(Suppl 121(6)):23–27.

26 Kimura Y, Weiss JE, Haroldson KL *et al*. Pulmonary hypertension and other potentially fatal pulmonary complications in systemic juvenile idiopathic arthritis. Arthritis Care Res 2013;65:745–52.

27 Kaneko Y, Kameda H, Ikeda K *et al*. Tocilizumab in patients with adult-onset still's disease refractory to glucocorticoid treatment: a randomised, double-blind, placebo-controlled phase III trial. Ann Rheum Dis 2018;77:1720–9.

28 Ma Y, Wu M, Zhang X *et al*. Efficacy and safety of tocilizumab with inhibition of interleukin-6 in adult-onset Still's disease: a meta-analysis. Mod Rheumatol 2018;28:849–57.

29 Hausmann JS. Targeting cytokines to treat autoinflammatory diseases. Clin Immunol 2019;206:23–32.

30 Kaplanski G. Interleukin-18: biological properties and role in disease pathogenesis. Immunol Rev 2018;281:138–53.

31 Nariai Y, Kamino H, Obayashi E *et al*. Generation and characterization of antagonistic anti-human interleukin (IL)-18 monoclonal antibodies with high affinity: two types of monoclonal antibodies against full-length IL-18 and the neoepitope of inflammatory caspase-cleaved active IL-18. Arch Biochem Biophys 2019;663:71–82.

32 D'Hoore W, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson comorbidity index with administrative data bases. J Clin Epidemiol 1996;49:1429–33.

33 Hintenberger R, Falkinger A, Danninger K, Pieringer H. Cardiovascular disease in patients with autoinflammatory syndromes. Rheumatol Int 2018;38:37–50.

34 Ridker PM. From C-reactive protein to interleukin-6 to interleukin-1: moving upstream to identify novel targets for atheroprotection. Circ Res 2016;118:145–56.

35 Ridker PM, Everett BM, Thuren T *et al*. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119–31.

36 Liao KP, Cai T, Gainer V *et al*. Electronic medical records for discovery research in rheumatoid arthritis. Arthritis Care Res 2010;62:1120–7.

37 Cai T, Lin TC, Bond A *et al*. The association between arthralgia and vedolizumab using natural language processing. Inflamm Bowel Dis 2018;24:2242–6.