PROTOCOL

Official Title

Development of a Prediction Model for the Risk of Hospitalized Infection in Patients With Chronic Inflammatory Arthritis Treated With Biological Drugs

Brief Title

Predicting Hospitalized Infection in Patients With Chronic Inflammatory Arthritis Treated With Biological Drugs

Authors

Simon Krabbe[1,2], Kathrine Grøn[1,2], Bente Glintborg[1], Mette Nørgaard[3], Frank Mehnert[3], Dorte Ejg Jarbøl[4], Nina Friis-Møller[5], Mikkel Østergaard[1,2], Merete Lund Hetland[1,2]

Affiliations

1 Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet

2 Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen

3 Department of Clinical Epidemiology, Aarhus University

4 Department of Public Health, University of Southern Denmark

5 Department of Infectious Diseases, Zealand University Hospital

Study Registration

The study will be registered on clinicaltrials.gov.

Conflicts of Interests

B.G. reported receiving funding from AbbVie and Biogen. All other authors report no relevant conflicts of interest with regards to this study.

Ethics Committee

This study does not require approval by Ethics Committee.

Data Approval

Approval to use data has been obtained from The Capital Region of Denmark (RH-2015-209).

Timeline

The merged dataset is expected to be ready for analysis in June 2018. The manuscript is expected to be submitted for publication in a peer-reviewed journal in December 2018.

Contributors

The protocol was drafted by S.K. and all authors critically revised it. All statistical analyses will be performed by S.K. The project was conceived by S.K., D.E.J., N.F.M., B.G. and M.L.H.

Acknowledgement

We thank Niels Steen Krogh, ZiteLab, for extracting the necessary data from DANBIO and all the Danish departments of rheumatology that report to DANBIO.

Brief Summary

Background

The risk for hospitalized infection (i.e. infection leading to hospitalization) in patients with inflammatory arthritis (rheumatoid arthritis (RA), psoriatic arthritis (PsA) or axial spondyloarthritis (axSpA) treated with biological drugs is known to be increased compared to the background population. In daily clinical practice, there is a need for a simple way to assess the absolute risk for hospitalized infection in individual patients based on easily available information such as age, diagnosis, functional status, comorbidities and medication. This risk estimate will be useful in clinical decision making e.g. when advising patients on whether or not to initiate biologic therapy or when advising patients on influenza or pneumococcal vaccination.

Objectives

The objectives are 1) to assess the risk for hospitalized infection (infection leading to hospitalization) in patients with inflammatory arthritis during 12 months of follow-up after initiating treatment with their first biological drug (bDMARD) with the risk in the general population, and 2) to develop a simple, clinically useful algorithm that allows prediction of the risk of hospitalized infection in individual patients.

Methods

Observational cohort study based on existing data in: The Danish Rheumatology Register (DANBIO), The Danish National Patient Register, The Danish National Prescription Register and The Danish Register of Causes of Death. All patients registered in DANBIO with RA, PsA or axSpA who initiated treatment with their first biological drug between January 1, 2006 and December 31, 2016 will be identified. Baseline predictors and outcomes (hospitalized infection or death) during 12 months of follow-up are obtained. Logistic regression analysis and 10-fold cross-validation will be used to develop and internally validate the prediction model.

Introduction

The risk of hospitalized infection in patients with inflammatory arthritis, here defined as rheumatoid arthritis (RA), psoriatic arthritis (PsA) or axial spondyloarthritis (axSpA), may be increased due to the immunosuppressive treatments. The seriousness of hospitalized infections is reflected by increased mortality. RA patients have an increased mortality compared to the general population, with more deaths caused by infections[1,2]. Similar results have been found in axSpA[3,4], whereas a single study in PsA found an infection-related mortality at the level of the general population[5].

In most studies, severe infection has been defined as hospitalized infection (i.e. infection leading to hospitalization). In patients with unselected inflammatory polyarthritis[6] and in patients with RA[7,8] a doubled risk of hospitalized infection was found compared to that of the general population. Risk of hospitalized infections varies across studies and across indications. For RA, the risk of severe infection according to the British Society for Rheumatology Biologics Register[9], the Swedish ARTIS Register[10], the German RABBIT Register[11] and the Canadian Ontario Health Insurance Plan[12] have all been in the range of 2-5 events per 100 patient years. Patients with axSpA had 1-2 severe infections per 100 patient years[13]; these patients were younger than in the RA studies. In one study of patients with PsA, the risk of opportunistic infections was higher than in the general population[14], but we are not aware of population-based observational studies of the overall risk of hospitalized infections in patients with PsA.

A model for the individual RA patient's risk of hospitalized infection based on age, functional status, selected comorbidities, glucocorticoid dose, and treatment has been developed based on data from the Germany RABBIT register[11]. This model has later been validated in the same registry during a later time period[15]. In routine care, such a prediction model would potentially be useful when advising the patient on vaccination. It has been suggested to vaccinate all patients with chronic inflammatory arthritis against influenza and pneumococcal disease[16], but in routine care vaccination uptake is low and it is costly to vaccinate all patients. The benefit for each patient depends on the absolute risk that the patient, if not vaccinated, would get the infectious disease. Thus, a more targeted approach of vaccinating only patients of moderate to high risk may be more cost-effective. This may also be assist in the decision making of whether to start a biological disease-modifying anti-rheumatic drug (bDMARD) in patients who are at high risk for hospitalized infection.

The RABBIT risk score has some potential drawbacks. Diabetes and cardiovascular diseases are common comorbidities that increase the risk of hospitalized infections in patients with chronic inflammatory arthrits[17,18], and smoking is also a predictor for hospitalized infections[6,9], but these variables were not included in the development of the RABBIT risk score. Also, when the age-related risk of hospitalized infections is modelled as a dichotomous variable using 60 years as cut-off, much predictive information based on different ages within the two broad age groups is likely to be lost.

The objectives are 1) to compare the risk for hospitalized infection in patients with inflammatory arthritis during 12 months of follow-up after initiating treatment with their first bDMARD with the risk in the general population, 2) to investigate if infection risk varies across diagnoses (RA/PsA/axSpA), and 3) to develop a simple, clinically useful algorithm that allows prediction of the risk of hospitalized infection in individual patients.

Methods

Study design

This is an observational registry-based study using data from the following Danish nationwide registries: The Danish Rheumatology Register (DANBIO)[19] (clinical data for patients with inflammatory rheumatic diseases), The Danish National Patient Register[20] (International Classification of Diseases ICD-10 codes for all contacts to hospitals), The Danish National Prescription Registry[21], and The Danish Register of Causes of Death[22].

Study population

We will identify three cohorts of patients in DANBIO with RA, SpA and PsA, respectively, who started treatment with the first bDMARD between January 1, 2006 and December 31, 2016 in Denmark. Patients will be identified based on the diagnosis recorded in DANBIO, which is known to be of high validity[23]. Index date is the date of start of first bDMARD.

Inclusion criteria:

- Patients with RA: Registered in DANBIO with a diagnosis of M05.9, M06.0 or M06.9.
- Patients with SpA: Registered in DANBIO with a diagnosis of M45.9, M46.1, M46.8+M02.9, M46.8+M07.4, M46.8+M07.5 or M46.9.
- Patients with PsA: Registered in DANBIO with a diagnosis of M07.3 or M46.8+M07.2.
- First bDMARD treatment course.
- Start of treatment with first bDMARD in the period January 1, 2006 to December 31, 2016.
- Age at start of treatment with first bDMARD ≥ 18 years.

Exclusion criteria:

- Not followed in DANBIO since start of first bDMARD.

Control group

For each cohort, a set of matched controls from the general population will be obtained, so that outcomes in each diagnosis group can be compared with its own matched controls. Therefore, 3 groups of matched controls are constructed. Ten controls from the general population will be drawn for each patient matched by age, sex and postal code (replacement is allowed). Index date equal to date of start of first bDMARD. At the index date, controls must not have or have had one the diagnoses of RA, SpA or PsA listed above. Baseline variables (predictors) and outcomes (for definitions and details, see below) will be collected in the same time periods for each individual patient and his/her 10 matched controls.

Exposure and follow-up time

For patients, the index date is the start date of the first bDMARD: abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, secukinumab tocilizumab or ustekinumab. End of follow-up is defined as 12 months after the index date for each patient, regardless of whether the bDMARD is discontinued during this period or not. This reflects the clinical situation: When the decision to start treatment with bDMARD is made, it is not known if the patient will continue or discontinue the bDMARD.

Baseline variables (predictors)

Baseline variables are collected from three registries: The Danish National Patient Register, The Danish National Prescription Registry, and DANBIO. The baseline variables include all variables in the RABBIT risk score[15], as well as other important predictors previously identified in other studies as predictors of severe infections[17,18]. Included variables should be readily available for a prediction algorithm applied in routine care. A few remarks on selected variables:

- Index of disease activity in patients with RA: Disease Activity Score 28 Joint Count (DAS28)
- Index of disease activity in patients with PsA: Disease Activity Index for Psoriatic Arthritis 28 Joint Count (DAPSA28, a modified version of DAPSA based on 28 joints instead of 66/68 joints)
- Indices of disease activity in patients with axSpA: Ankylosing Spondylitis Disease Activity Score (ASDAS) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- Diabetes yes/no: Subjects are defined as having diabetes if fulfilling the codes (**Table 1**) in the National Patient Register and/or having ≥2 separate purchases of drugs used in diabetes from baseline and 5 years back according to the Danish National Prescription Registry[21] (**Table 2**). This follows the algorithm in the Danish National Diabetes Register[24], except that patients with only multiple blood sugar measurements or a referral to podiatric care will not be included.
- Lung disease yes/no: Subjects are defined as having asthma, chronic obstructive pulmonary disease, interstitial pulmonary disease or bronchiectasis if fulfilling the codes in The Danish National Patient Register (**Table 1**) or having ≥2 separate purchases of drugs for obstructive airway diseases from baseline and 5 years back according to The Danish National Prescription Register (**Table 2**). This is in line with the approach used in the Danish National Database for Asthma[25], except that we allow age >44 years and do not discriminate between asthma and COPD, as this was not deemed possible in this context. Therefore all diagnoses of obstructive airway diseases in The Danish National Patient Registry, as well as interstitial lung disease and bronchiectasis, will be included.
- Systemic or intraarticular glucocorticoids yes/no: Data on glucocorticoids will be merged from The Danish National Prescription Register (**Table 2**) and DANBIO (**Table 3**) into a single variable that indicates whether the patient has received more than a trivial amount of glucocorticoids, i.e. one of the following: A) injection at ≥2 separate dates from baseline and 12 months back and >2 mL in total, B) use of oral glucocorticoids registered in DANBIO from baseline and 12 months back, or C) ≥2 purchases of prednisolone for systemic use from baseline and 12 months back.

Further details of all baseline variables for patients and matched controls are shown in **Tables 1-3**.

Table 1. Baseline variables identified in The Danish National Patient Register (patients and matched controls)

Variable	Description	Comment	Values
Malignancy, within 10 years	C00-C43, C45-C96	Time: from baseline and 10 years back	yes/no
Malignancy, ever	C00-C43, C45-C96	Time: At any time before baseline	yes/no
Hospitalized infection within 5 years	A00-B99, D73.3, E06.0, E32.1, G00-G02, G04.2, G05-G07, H00.0, H44.0, H60.0-H60.3, H66-H67, H70, I30.1, I40.0, J00-J22, J32, J34.0, J36, J38.3, J39.0-J39.1, J44.0, J85, J86, K04.4, K04.6, K04.7, K10.2, K11.3, K12.2, K14.0, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.1, K65.2, K65.9, L00-L08, L30.3, M00-M01, M46.2-M46.5, M60.0, M65.0, M71.0, M71.1, M72.6, M86, N10, N11, N12, N13.6, N15.1, N15.9, N30.0, N30.8, N34.0, N39.0, N41.2, N43.1, N45.2, N45.3, N45.4, N48.2, N61, N70, N73, N75.1, O23, O26.4, O41.1, O75.3, O85, O86, O88.3, O91, O98	Time: from baseline and 5 years back	yes/no
Knee or hip prosthesis within 5 years	NGB, NFB	Time: from baseline and 5 years back	yes/no
Lung disease within 5 years	J41-J45, J47, J84.1, J84.9	Time: from baseline and 5 years back	yes/no
Diabetes within 5 years	E10-E14, O24	Time: from baseline and 5 years back	yes/no
Myocardial infarction within 5 years	I20.0, I21, I22	Time: from baseline and 5 years back	yes/no
Chronic kidney disease within 5 years	I12, I13, N00-N05, N07, N11, N18-N19, Q61	Time: from baseline and 5 years back	yes/no
Inflammatory bowel disease within 5 years	K50, K51	Time: from baseline and 5 years back	yes/no
International Classification of Diseases ICD-10 codes for all diseases listed. For surgical procedures (knee or hip prosthesis), the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures is used.			

Table 2. Baseline variables identified in The Danish National Prescription Register (patients and matched controls)

Variable	Description	Comment	Value
Drugs used in diabetes	ATC: A10	Time: ≥2 separate purchases from baseline and 5 years back	yes/no
Drugs for obstructive airway diseases	ATC: R03	Time: ≥2 separate purchases from baseline and 5 years back	yes/no
Corticosteroids for systemic use at baseline	ATC: H02	Time: ≥2 separate purchases from baseline and 12 months back	yes/no

Table 3. Baseline variables from DANBIO (only patients)

Variable	Description	Comment	Value
Social security number			
Gender			male/female
Specific diagnosis code	ICD-10 Code in DANBIO		
Date of start of symptoms			Date (MM/YYYY)
Date of diagnosis			Date (MM/YYYY)
bDMARD – drug name	Orencia/Abatacept, Humira/Adalimumab, Kineret/Anakinra, Cimzia/Certolizumab pegol, Enbrel/Etanercept, Benepali/Etanercept, Simponi/Golimumab, Remicade/Infliximab, Inflectra/Infliximab, Remsima/Infliximab,	First biological drug	Character (”abatacept”, ”adalimumab”, ”anakinra”, ”certolizumab”,

	MabThera/Rituximab, Cosentyx/Secukinumab, RoActemra/Tocilizumab, Stelara/Ustekinumab		”etanercept”, ”golimumab”, ”infliximab”, ”rituximab”, ”secukinumab”, ”tocilizumab”, ”ustekinumab”)
bDMARD – start date		First biological drug	Date (DD/MM/YYYY)
csDMARD – drug name	Methotrexate, sulphasalazine, hydroxychloroquine, leflunomide	Only if csDMARD was given at baseline	Character (“methotrexate”, “sulphasalazine”, “hydroxychloroquine”, “leflunomide”)
csDMARD – start date		Only if csDMARD was given at baseline	Date (DD/MM/YYYY)
Oral glucocorticoids		Time: from baseline and 12 months back	yes/no
Glucocorticoid injections (intramuscular or intraarticular)		Time: injection at ≥2 separate dates from baseline and 12 months back and >2 mL in total	yes/no
Health Assessment Questionnaire (HAQ)		At baseline (as close to baseline as possible, up to 12 months before is allowed)	Numeric (range 0-3)
C-reactive protein		Time: from baseline and 90 days back or 6 days after	
Disease activity	Separate columns for DAS28, DAPSA28, ASDAS, BASDAI	Time: from baseline and 90 days back or 6 days after	Numeric
Smoking status		At baseline (first, this should be searched back in time from baseline and data closest to baseline should be used; if no data are found back in time, data on smoking status will be searched from baseline and onwards)	Character (“current”, “occasionally”, “previous”, “never”)
Number of csDMARD treatment failures	Number of previously received DMARDs that the patient no longer receives at baseline (stop date at baseline date or before). If a patient switches from oral to subcutaneous methotrexate it is not counted as a treatment failure. If a patient stops a drug and starts it again within ≤3 months, the first stop is not counted as a treatment failure; however, if the patient received another csDMARD in the intervening period, the first treatment period will count as a failure. The patient can only fail each drug once.	Before baseline	Integer

Outcomes

Hospitalized infections are defined as hospitalization caused by infection according to The Danish National Patient Register (**Table 4**). Overall mortality and cause-specific mortality are identified in The Danish Register of Causes of Death (**Table 5**). The risk of hospitalized infection, overall mortality and mortality caused by infection will be calculated for the 12 months of follow-up after start of treatment with the first biological DMARD. Each patient will be counted as either having an event (hospitalized infection and/or death from any cause) or not during the 12 month of follow-up. The number of deaths is expected to be very low.

Table 4. Outcome variables identified in National Patient Register (patients and matched controls)			
Variable	Description	Comment	Values
Hospitalized infections during 12 months of follow-up	A00-B99, D73.3, E06.0, E32.1, G00-G02, G04.2, G05-G07, H00.0, H44.0, H60.0-H60.3, H66-H67, H70, I30.1, I40.0, J00-J22, J32, J34.0, J36, J38.3, J39.0-J39.1, J44.0, J85, J86, K04.4, K04.6, K04.7, K10.2, K11.3, K12.2, K14.0, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.1, K65.2, K65.9, L00-L08, L30.3, M00-M01, M46.2-M46.5, M60.0, M65.0, M71.0, M71.1, M72.6, M86, N10, N11, N12, N13.6, N15.1, N15.9, N30.0, N30.8, N34.0, N39.0, N41.2, N43.1, N45.2, N45.3, N45.4, N48.2, N61, N70, N73, N75.1, O23, O26.4, O41.1, O75.3, O85, O86, O88.3, O91, O98	Visits to emergency room (Danish: "skadestue") are not included. If a patient is discharged from hospital and is at home one night, it counts as one hospitalization. If the patient is hospitalized the day after, it counts as a new hospitalization. Patients that are seen as outpatients (Danish: "ambulante kontakter") are not included.	All primary and contributory diagnoses (ICD-10 codes), admission and discharge dates for all hospitalizations with infection as primary diagnosis during 12 months of follow-up. If the primary diagnosis is RA, SpA or PsA, then infection should also be searched for in the secondary diagnoses.

Table 5. Outcome variables identified in The Danish Register of Causes of Death (patients and matched controls)			
Variable	Description	Comment	Values
Cause of death	Information on all deaths		As appropriate
Mortality is ascribed to infection if any of the diagnoses in Table 4 are entered on the death certificate in any data field (direct cause, underlying cause, or contributing cause).			

Statistical analysis

The expected number of patients to be included is 7,500. The expected number of patients with at least one hospitalized infection during the 12 months of follow-up is 300, based on incidence rates previously published.

The number of participants with hospitalized infection or death during the 12 months of follow-up will be compiled for each diagnosis group (RA, SpA, PsA) stratified by age. Age will be categorized as <40 years, 40-49 years, 50-59 years, 60-69 years, ≥70 years (this may need to be adapted based on the observed number of events).

The crude risk of hospitalized infections will be calculated in the 6 groups (RA-bDMARD, SpA-bDMARD, PsA-bDMARD and the 3 groups of matched controls) stratified by age as the 12-month risk of any hospitalized infection with 95% confidence intervals. The risk in each patient group, stratified by age, will be compared to the risk for its matched controls as risk difference (absolute risk) and risk ratio (relative risk).

Multivariable logistic regression will be performed to develop the prediction model. Missing values of predictor variables will be imputed after an analysis of possible patterns of missing data. Unless otherwise indicated, multiple imputation by chained equations (MICE) will be performed under the assumption that data are missing at random. Baseline age and comorbidities (yes/no, as described in methods section above: malignancy, previous hospitalized infection, knee or hip prosthesis, lung disease, diabetes, myocardial infarction, chronic kidney disease and inflammatory bowel disease), will be included in the model. We aim to develop a simple prediction algorithm for the risk of hospitalized infection based on the results from the stratified analysis and the multivariable regression analysis.

The model form will be built gradually and improved based on the data. The performance will be evaluated by the overall explained variation, ROC curve and calibration plot, and it will be internally validated using 10-fold cross-validation. The regression formula of the final model and, possibly, a simple presentation in the form of a score chart or a table with predictions will be provided.

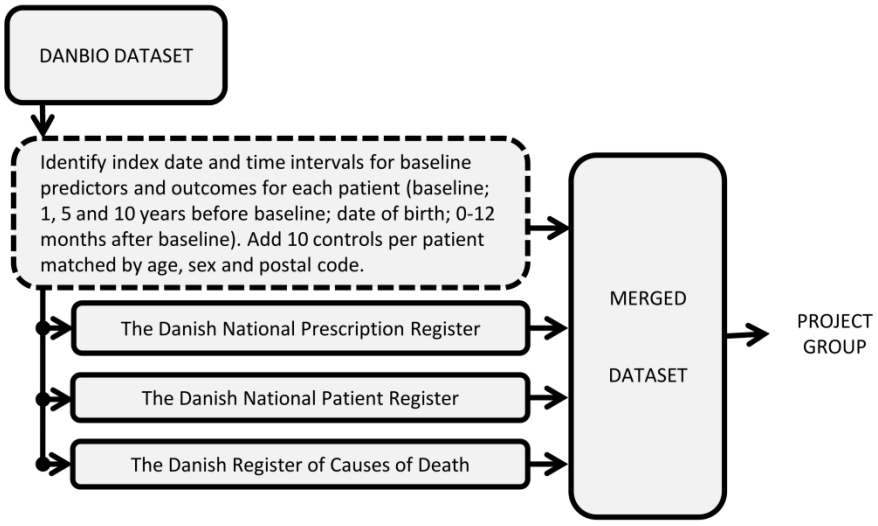
If the number of hospitalized infections is sufficiently large, an analysis of different sites of infection may be performed (e.g. pneumonia/respiratory tract infections, skin/subcutaneous tissue/musculoskeletal system infection, genitourinary tract infections, infections of the gastrointestinal tract, sepsis, and other infections).

Complete case analysis (patients with no missing data that have to be imputed) will be performed as sensitivity analysis. It is possible that the case mix of patients treated with bDMARD may change over time, and a sensitivity analysis of the effect of calendar years will be performed.

It is possible that separate prediction models are needed for each of the 3 disease groups. However, if no major differences exist between the infection risks in the 3 disease groups across age, comorbidities and glucocorticoid use, a single model will be chosen.

Data flow

This figure shows the data flow to create the final merged dataset.



Department of Clinical Epidemiology, Aarhus University, receives the DANBIO dataset, identifies 10 matched controls per patient, collects data from other registries and creates merged dataset.

Results

During data analysis, **Tables 6-11** will be produced.

Table 6. Baseline characteristics (separate tables for RA patients, SpA patients and PsA patients)

		Rheumatoid arthritis		General population	
		Available data		Available data	
Number of patients/controls	Number				
Age, years	Median, IQR				
Male/female	%/%				
Duration of symptoms, years	Median, IQR			NA	NA
Disease duration (after diagnosis), years	Median, IQR			NA	NA
Methotrexate	%			NA	NA
Other csDMARDs (sulfasalazine, hydroxychloroquine, leflunomide)	%			NA	NA
Oral glucocorticoids for systemic use at baseline	% / Median, IQR				
Injections of glucocorticoids for systemic use at baseline	% / Median, IQR			NA	NA
TNF inhibitor/other bDMARD	%/%			NA	NA
Number of previous DMARD treatment failures	%			NA	NA
Smoking status: Current/Occasionally/Previous/Never	%/%/%/%			NA	NA
Health Assessment Questionnaire (HAQ)	Median, IQR			NA	NA
Malignancy, within 10 years	%				
Malignancy, ever	%				
Hospitalized infection, within 5 years	%				
Knee or hip prosthesis, within 5 years	%				
Lung disease, within 5 years	%				
Diabetes, within 5 years	%				
Myocardial infarction, within 5 years	%				
Chronic kidney disease, within 5 years	%				
Inflammatory bowel disease, within 5 years	%				

Table 7. Risk of hospitalized infection by disease

	RA	SpA	PsA	Matched controls for RA patients	Matched controls for SpA patients	Matched controls for PsA patients
No. of patients/controls						
No. of patients/controls with at least one hospitalized infection, n						
Risk of hospitalized infection (95% CI)						
Risk difference[1]				NA	NA	NA
Risk ratio[1]				NA	NA	NA
[1]Compared to the general population, matched for age, sex and postal code.						

Table 8. Risk of hospitalized infection by age (separate tables for RA patients, SpA patients and PsA patients)

	<40 years	40-50 years	50-60 years	60-70 years	>70 years
No. of patients					
No. of patients with at least one hospitalized infection, n					
Risk of hospitalized infection (95% CI)					
Risk difference[1]					
Risk ratio[1]					
[1]Compared to the general population, matched for age, sex and postal code.					

Table 9. Risk of hospitalized infection by comorbidities (separate tables for RA patients, SpA patients and PsA patients)			
	No comorbidities	1 comorbidity	2 or more comorbidities
No. of patients			
No. of patients with at least one hospitalized infection, n			
Risk of hospitalized infection (95% CI)			
Risk difference[1]			
Risk ratio[1]			
Comorbidities are: Malignancy, previous hospitalized infection, knee or hip prosthesis, lung disease, diabetes, myocardial infarction, chronic kidney disease and inflammatory bowel disease. [1]Compared to the general population, matched for age, sex and postal code.			

Table 10. Risk of hospitalized infection by glucocorticoid use (separate tables for RA patients, SpA patients and PsA patients)		
	No glucocorticoids	Glucocorticoids*
No. of patients		
No. of patients with at least one hospitalized infection, n		
Risk of hospitalized infection (95% CI)		
Risk difference[1]		
Risk ratio[1]		
* One of the following: A) injection at ≥2 separate dates from baseline and 12 months back and >2 mL in total, B) use of oral glucocorticoids registered in DANBIO from baseline and 12 months back, C) ≥2 purchases of corticosteroids for systemic use from baseline and 12 months back. [1]Compared to the general population, matched for age, sex and postal code.		

Table 11. All-cause mortality and cause-specific mortality due to infection			
	RA	SpA	PsA
No. of patients			
No. of all deaths, n			
Mortality rate (all-cause)			
Standardized mortality rate (all-cause)			
No. of deaths due to infection, n			
Mortality rate (infection)			
Standardized mortality rate (infection)			

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