A nationwide population-based cohort study of the incidence of severe and rare infections among adults with psoriasis in Denmark*

Nikolai Loft,1 Lone Skov,1 Craig Richardson,2 Vivek Trivedi,3 Ivette Alarcon2 and Alexander Egeberg4

1Department of Dermatology and Allergy, Copenhagen University Hospital – Herlev and Gentofte, Gentofte, Denmark
2Novartis Pharma AG, Basel, Switzerland
3Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA
4Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark

Abstract

Background Patients with psoriasis have a high risk for multiple comorbid conditions. However, few studies have examined the association between psoriasis and severe and rare infections. This study reports the incidence of severe and rare infections (considered as rare in Denmark) among Danish patients with psoriasis, compared with the general population.

Objectives The objectives of this study were to assess the incidence and risk of severe and rare infections in Danish patients with psoriasis and the matched general population, and to compare this risk for patients with severe or mild psoriasis with that of the general population.

Methods Data for individuals aged ≥18 years who were alive and resident in the source population were collected from the Danish National Patient Register between 1 January 1997 and 31 December 2018. Individuals with any of the investigated chronic infections prior to inclusion were excluded. Patients with psoriasis were matched (1 : 6) for age and sex with general population controls. Severe infections were defined as infections requiring treatment in a hospital setting and rare infections included HIV, hepatitis B and C, and tuberculosis infections. Incidence rates (IRs) were reported per 100 000 person-years of exposure. Severe psoriasis was defined according to previous or active use of systemic treatment. Patients who never received biological and/or systemic treatment were categorized as having mild psoriasis.

Results A total of 94 450 patients with psoriasis were matched with 566 700 controls. The respective IRs were higher for patients with any psoriasis compared with controls; IR 3104 (95% CI 3066 to 3143) and IR 2364 (95% CI 2330 to 2394) for any infection, IR 3080 (95% CI 3046 to 3119) and IR 2381 (95% CI 2351 to 2411) for severe infections. Patients with severe psoriasis had higher IRs (1 : 6) for age and sex with general population controls. Severe infections were defined as infections requiring treatment in a hospital setting and rare infections included HIV, hepatitis B and C, and tuberculosis infections. Incidence rates (IRs) were reported per 100 000 person-years of exposure. Severe psoriasis was defined according to previous or active use of systemic or biological treatment. Patients who never received biological and/or systemic treatment were categorized as having mild psoriasis.

Conclusions As the severity of psoriasis increases, so does the risk of severe and rare infections. Therefore, clinicians should be aware of the increased risk of severe and rare infections in patients with severe psoriasis so that early investigation and treatment can be initiated.
Psoriasis is a common chronic, immune-mediated inflammatory disease that affects 2 to 4% of the population in Western countries.\textsuperscript{1,2} Psoriasis is characterized by lesional skin exhibiting red plaques with silver or white scales and disease pathogenesis is driven by a network of leukocytes and cytokines.\textsuperscript{3} The global burden of psoriasis is large, both in terms of impact on quality of life for patients\textsuperscript{4} and healthcare costs.\textsuperscript{5–7}

Patients with psoriasis are known to be at higher risk for multiple comorbid conditions, including psoriatic arthritis, nonalcoholic steatohepatitis, cardiovascular disease and certain types of cancer.\textsuperscript{8–17} Previous studies have also found that patients with psoriasis have an increased risk of serious infections (associated with hospitalization, pneumonia and herpes zoster).\textsuperscript{18–20} A UK population-based cohort study from 2020 describes the risk of hospitalization and death resulting from infection in people with psoriasis and found associations with small increases in risk for any infection, respiratory infections and soft tissue and skin infections.\textsuperscript{21} Additionally, patients with psoriasis are often treated with immunosuppressive therapies, which may lead to or aggravate infections. Thus, the potential association between psoriasis and risk of incidence of infections is important. However, few studies have assessed the incidence and risk of severe infections and rare infections, the latter of which, in Denmark, includes tuberculosis (TB), hepatitis B (HBV) and hepatitis C (HCV) and HIV, among patients with psoriasis with different disease severities.\textsuperscript{12–20}

There is currently limited real-world evidence regarding the occurrence and risk of severe and rare infections among patients with psoriasis. Furthermore, certain treatments for psoriasis may aggravate infections. Therefore, the current nationwide population-based cohort study aimed to investigate Danish nationwide administrative longitudinal registries for descriptive data on the incidence of severe infections and infections considered rare in Denmark among individuals with different psoriasis disease severities and matched individuals from the general population. Additionally, the risk for all patients with mild or severe psoriasis was compared with that of the general population.

\[\text{What is already known about this topic?}\]
- Few studies have looked at the incidence and prevalence of serious infections (associated with hospitalization) and rare infections including tuberculosis, hepatitis B and C, and HIV among patients with different severities of psoriasis.

\[\text{What does this study add?}\]
- Patients with psoriasis have an increased risk of severe and rare infections.
- Clinicians should be aware of the increased risk of severe and rare infections in patients with severe psoriasis so that early investigation and treatment can be initiated.

\[\text{Materials and methods}\]

\[\text{Study design and setting}\]

In this population-based cohort study, descriptive data were obtained from Danish administrative registries for residents in Denmark and were linked using the Civil Registration System.\textsuperscript{22} Collected data were linked using a unique numerical identification assigned to all Danish residents since 1968.\textsuperscript{22} National data on drug use in Denmark were extracted from the Danish National Prescription Database.\textsuperscript{23} This registry contains complete information, from 1 January 1995 onwards, on all prescriptions dispensed to Danish residents at community pharmacies. Registered drugs are categorized according to the Anatomical Therapeutic Chemical Classification System, a hierarchical classification developed by the World Health Organization for purposes of drug-use statistics. The Danish National Prescription Database is reported to have a high level of completeness and validity.\textsuperscript{24} Medical data from inpatient and outpatient hospital clinics, including medication and treatment procedures (e.g. medication given during hospitalization or given directly from the outpatient clinics, or phototherapy treatments) were extracted from the Danish National Patient Register,\textsuperscript{25} which contains nationwide data on hospital admissions since 1977 and outpatient contacts since 1995. In this registry, discharge and contact diagnoses are coded according to the International Classification of Diseases (ICD) 8th revision (ICD-8) from 1977 to 1993, and according to the ICD 10th revision (ICD-10) since 1994, noting that ICD-9 was never utilized.

Participants

All individuals in the entire Danish population aged ≥18 years between 1 January 1997 and 31 December 2018 were identified. To be eligible for inclusion in the study, individuals had to be alive and resident in the source population and have at least 1 day of follow-up. Individuals with any of the investigated chronic infections prior to inclusion were excluded. As
study cases, we identified all individuals with at least one diagnosis of psoriasis (ICD-10 diagnosis code L40.0 or L40.9) in the Danish National Patient Register during the study period or those who had filled a minimum of two prescriptions of calcipotriol (Anatomical Therapeutic Chemical code D05AX02 or D05AX52). Patients were followed from the date of first recorded psoriasis diagnosis or second calcipotriol prescription during the study period until the first of either death, migration, the occurrence of an endpoint, or 31 December 2018. Each patient with psoriasis was matched for sex and exact date of birth with six individuals from the general population in Denmark, using incidence density sampling. Furthermore, patients were stratified by psoriasis severity according to treatment with systemics, including biologics, for psoriasis (Table S1; see Supporting Information). The category of patients with ‘any’ type of psoriasis included all cases irrespective of severity. Patients with severe psoriasis were patients treated with systemic agents for psoriasis, and patients with mild psoriasis were those who were not treated with any of these agents. Psoriasis severity was included as a time-dependent variable and patients with severe psoriasis were considered as having severe psoriasis from the prescription date of the first prescribed systemic agent. This was in accordance with the newly proposed categorization of psoriasis severity from the International Psoriasis Council (IPC). The diagnosis of psoriasis has been validated in the Danish National Patient Register, with an overall positive predictive value (PPV) of 97% (98.0% in adults and 94.6% in children) based on medical chart reviews. The diagnosis of psoriasis based on prescription of calcipotriol has been validated with a PPV of 83.3% in adults.

**Study outcomes**

The outcomes of the current study were occurrences of severe and/or rare infections. Rare infections included HIV, TB, HBV and HCV. Severe infections were defined as infections requiring assessment at a hospital department (both inpatients and outpatients); the full list of infections is provided in Table S2 (see Supporting Information). The list of infections was based on previous studies in atopic dermatitis and inflammatory bowel diseases (IBDs). In a subanalysis, infections were limited to infections leading to hospitalization (inpatients only).

**Statistical analysis**

Population statistics were obtained and linked by Statistics Denmark, a governmental institution that collects and maintains data. Descriptive data were tabulated for patients with psoriasis and the matched general population. Incidence rates (IRs) are reported per 100 000 person-years and presented with 95% confidence intervals (CIs). Summary statistics were generated and expressed as mean for normally distributed variables, median and interquartile range (IQR) for nonnormally distributed continuous variables, and frequency for categorical variables. For age, both mean (SD) and median (IQRs)

were presented, to give a more detailed impression of the subgroup distribution. Analyses were carried out for all patients with psoriasis, stratified by severity (mild and severe), and in the general population. Cox proportional hazards regression models with calendar time as the underlying timescale were used to estimate hazard ratios (HRs) for the association between psoriasis and the infections. In the adjusted model, the adjusted HRs (aHRs) were adjusted for sex, age, ethnicity, socioeconomic status, alcohol-related conditions and Charlson Comorbidity Index. Cox proportional hazard regressions were used to compare all severities of psoriasis with the matched general population. Subanalyses were conducted according to psoriasis severity, comparing those with mild or severe psoriasis with the matched general population.

**Results**

**Participants**

A total of 94 450 patients with psoriasis and 566 700 general population reference individuals matched for age and sex were included in this study. General study cohort characteristics are shown in Table 1. The median age was 52.3 years (IQR 38.3–64.0), 50.1% were women, and 28.4% had more than one comorbidity. The majority of patients had not received any systemic therapy for psoriasis (57.3% were treated with topical agents only).

| Characteristic | Reference (N = 566 700) | Psoriasis (N = 94 450) |
|---------------|-------------------------|------------------------|
| Female sex    | 284 340 (50.2%)         | 47 390 (50.2%)         |
| Age, years, median (IQR) | 52-3 (38-3–64-1)        | 52-3 (38-3–64-1)       |
| Mean (SD)     | 51-5 (17-0)             | 51-5 (17-0)            |
| Mild psoriasis| –                       | 85 389 (90.4%)         |
| Severe infections | 118 059 (20-8)         | 24 742 (26-2)          |
| Rare infections | 1761 (0.3)             | 396 (0.4)              |
| Socioeconomic status |                   |                       |
| Lowest        | 114 515 (20-2)          | 17 716 (18-8)          |
| Below average | 113 138 (20-0)          | 19 091 (20-2)          |
| Average       | 113 164 (20-0)          | 19067 (20-2)           |
| Above average | 113 321 (20-0)          | 18 908 (20-0)          |
| Highest       | 112 562 (19-9)          | 19 668 (20-8)          |
| Alcohol-related conditions |               | 24 676 (4-4)           |
| Charlson Comorbidity Index |               | 5468 (5-8)            |

| Specific comorbidities | Reference (N = 566 700) | Psoriasis (N = 94 450) |
|------------------------|-------------------------|------------------------|
| COPD                   | 12 731 (2-3)            | 3111 (3-3)             |
| Hypertension           | 69 951 (12-3)           | 14 622 (15-5)          |
| Hyperlipidaemia        | 66 008 (11-7)           | 13 313 (14-1)          |
| Ischaemic heart disease| 30 731 (5-4)            | 6603 (7-0)             |
| DM2                    | 24 655 (4-4)            | 5855 (6-2)             |

COPD, chronic obstructive pulmonary disease; DM2, type 2 diabetes mellitus; IQR, interquartile range. Data are presented as n (%) unless otherwise stated.
Among patients with any type of psoriasis, the IR of any severe infections per 100 000 person-years among patients with any psoriasis was 1925 (95% CI 1520 to 2367), compared with 1531 (95% CI 1229 to 1892) among patients with any psoriasis (95% CI) 1531 to 1892 among patients with any psoriasis, compared with the matched general population was 1 to 62 (Figure 2) and the aHR for patients with severe psoriasis compared with the matched general population was 1.26 (95% CI 1.25 to 1.28) (Figure 1 and Table S5; see Supporting Information). When infections were limited to only those infections leading to hospitalization, it resulted in an IR of 1925 (95% CI 1892 to 1959) among patients with mild psoriasis, with similar HRs for infections overall (Table S6; see Supporting Information).

Patients with mild psoriasis

The IR of any infections among patients with mild psoriasis (IR 3003-5, 95% CI 2964-1 to 3043-4) was higher than in the control group (Table S4), and the aHR for patients with mild psoriasis compared with the matched general population was 1.26 (95% CI 1.25 to 1.28) (Figure 1 and Table S5; see Supporting Information). When infections were limited to only those infections leading to hospitalization, it resulted in an IR of 1925 (95% CI 1892 to 1959) among patients with mild psoriasis, with similar HRs for infections overall (Figure 2 and Table S9; see Supporting Information).

Incidence rates of any severe infections

Patients with psoriasis

Among patients with any psoriasis, the IR of any severe infections was higher at 3080.6 (95% CI 3042.5 to 3119.3) compared with 2364.4 (95% CI 2350.9 to 2377.9) for the control group (Table 2). Pulmonary, gastrointestinal, and urinary tract infections were less common among patients with psoriasis compared with the matched general population.

Table 2: Infections among the general population and patients with any psoriasis

| IR per 100 000 person-years among the general population (95% CI) | IR per 100 000 person-years among patients with any psoriasis (95% CI) | IR differences per 100 000 person-years (95% CI) |
|---------------------------------------------------------------|---------------------------------------------------------------|--------------------------------------------------|
| Any infections (rare or severe)                              |                                                               |                                                  |
| Any severe infections                                        | 2364-4 (2350-9 to 2377-9)                                     | 3080-6 (3042-5 to 3119-3)                        |
| CNS infections                                               | 21-29 (20-12 to 22-55)                                        | 29-65 (26-34 to 33-28)                           |
| URTI                                                        | 127-20 (124-26 to 130-21)                                     | 173-68 (165-36 to 182-42)                        |
| Pulmonary infections                                         | 772-53 (765-16 to 779-98)                                     | 984-21 (963-90 to 1005-01)                       |
| Heart infections                                             | 34-72 (32-00 to 36-30)                                        | 45-05 (40-92 to 49-59)                           |
| GI infections                                                | 565-04 (558-73 to 571-42)                                     | 718-21 (700-84 to 746-01)                        |
| UTI                                                         | 456-33 (450-69 to 462-03)                                     | 564-98 (549-70 to 580-67)                        |
| Gynecological infections                                     | 44-01 (41-59 to 46-57)                                        | 53-97 (47-63 to 61-16)                           |
| Musculoskeletal infections                                   | 55-94 (53-99 to 57-94)                                        | 82-96 (77-28 to 89-05)                           |
| Skin and subcutaneous tissue infections                      | 337-18 (332-33 to 342-09)                                     | 502-94 (488-48 to 517-82)                        |
| Opportunistic infections                                     | 86-91 (84-48 to 89-39)                                        | 115-33 (108-59 to 122-48)                        |
| Other infections                                             | 280-60 (276-20 to 285-06)                                     | 381-85 (369-38 to 394-74)                        |
| Sepsis                                                      | 240-74 (236-68 to 244-87)                                     | 335-40 (323-75 to 347-46)                        |

CI, confidence interval; CNS, central nervous system; GI, gastrointestinal; IR, incidence rate; URTI, upper respiratory tract infections; UTI, urinary tract infections.

Incidence rates of any infections (severe and rare)

Patients with any type of psoriasis

Among patients with any type of psoriasis, the IR of any infection (severe and rare) per 100 000 person-years was higher at 3104.9 (95% CI 3066-6 to 3143-7) compared with 2381-1 (95% CI 2367-6 to 2394-6) for the control group (Table 2). The crude HR for patients with psoriasis and the age- and sex-matched general population (control group) was 1.31 (95% CI 1.29 to 1.33) and the HR adjusted for sex, age, ethnicity, socioeconomic status, alcohol-related conditions and Charlson Comorbidity Index (aHR) was 1.29 (95% CI 1.27 to 1.31) (Table 3 and Figure 1). When infections were limited to only those infections leading to hospitalization (inpatients only), it resulted in a higher IR of 2037-7 (95% CI 1973-0 to 2037-7) among patients with any psoriasis, compared with 1531-8 (95% CI 1520-6 to 1543-0) among the control group (Table 4), and demonstrated similar HRs (Figure 2 and Table S3; see Supporting Information).

Patients with mild psoriasis

The IR of any infections among patients with mild psoriasis (IR 3003-5, 95% CI 2964-1 to 3043-4) was higher than in the control group (Table S4), and the aHR for patients with mild psoriasis compared with the matched general population was 1.26 (95% CI 1.25 to 1.28) (Figure 1 and Table S5; see Supporting Information). When infections were limited to only those infections leading to hospitalization, it resulted in an IR of 1925 (95% CI 1892-8 to 1959-1) among patients with mild psoriasis, with similar HRs for infections overall (Table S6; see Supporting Information).

Patients with severe psoriasis

The IR among patients with severe psoriasis (IR 3847-7, 95% CI 3754-3 to 3943-4) was higher than that found in the control group (Table 5); and the aHR for patients with severe psoriasis compared with the matched general population was 1.58 (95% CI 1.54–1.62) (Figure 1 and Table S7; see Supporting Information). When infections were limited to only those infections leading to hospitalization, it resulted in an IR of 2535-2 (95% CI 2456-2 to 2616-8) among patients with severe psoriasis (Table S8; see Supporting Information), with similar HRs for infections overall (Figure 2 and Table S9; see Supporting Information).

Incidence rates of any severe infections

Patients with psoriasis

Among patients with any psoriasis, the IR of any severe infections was higher at 3080.6 (95% CI 3042.5 to 3119.3) compared with 2364.4 (95% CI 2350-9 to 2377-9) for the control group (Table 2). Pulmonary, gastrointestinal, and urinary tract infections were less common among patients with psoriasis compared with the matched general population.

to 64-1), and 50-2% of the study cohort were female. Several comorbidities were more prevalent in patients with psoriasis compared with the general population (Table 1).
### Table 3 Infections among the general population and patients with any psoriasis

| Infections                        | Patient-years at risk | Number of events | HR (95% CI) crude | p-values | HR (95% CI) adjusted* | p-values |
|-----------------------------------|-----------------------|------------------|-------------------|----------|------------------------|----------|
| **Any infections (rare or severe)** |                       |                  |                   |          |                        |          |
| Reference                         | 4 987 540             | 118 756          | -                 | -        | -                      | -        |
| Psoriasis                         | 801 860               | 24 897           | 1.31 (1.29–1.33)  | < 0.0001 | 1.29 (1.27–1.31)       | < 0.0001 |
| **Severe infections**            |                       |                  |                   |          |                        |          |
| Reference                         | 4 993 240             | 118 059          | -                 | -        | -                      | -        |
| Psoriasis                         | 803 150               | 24 742           | 1.31 (1.29–1.32)  | < 0.0001 | 1.29 (1.27–1.31)       | < 0.0001 |
| **CNS infections**               |                       |                  |                   |          |                        |          |
| Reference                         | 5 545 840             | 118 1           | -                 | -        | -                      | -        |
| Psoriasis                         | 924 040               | 274              | 1.39 (1.22–1.59)  | < 0.0001 | 1.37 (1.20–1.56)       | < 0.0001 |
| **URTI**                          |                       |                  |                   |          |                        |          |
| Reference                         | 5 518 200             | 7019             | -                 | -        | -                      | -        |
| Psoriasis                         | 917 770               | 1594             | 1.37 (1.30–1.45)  | < 0.0001 | 1.36 (1.29–1.43)       | < 0.0001 |
| **Pulmonary infections**         |                       |                  |                   |          |                        |          |
| Reference                         | 5 404 440             | 41 751           | -                 | -        | -                      | -        |
| Psoriasis                         | 892 900               | 8788             | 1.28 (1.25–1.31)  | < 0.0001 | 1.25 (1.22–1.28)       | < 0.0001 |
| **Heart infections**             |                       |                  |                   |          |                        |          |
| Reference                         | 5 542 010             | 1924             | -                 | -        | -                      | -        |
| Psoriasis                         | 923 450               | 416              | 1.30 (1.17–1.44)  | < 0.0001 | 1.26 (1.13–1.40)       | < 0.0001 |
| **GI infections**                |                       |                  |                   |          |                        |          |
| Reference                         | 5 393 260             | 30 474           | -                 | -        | -                      | -        |
| Psoriasis                         | 892 640               | 6411             | 1.27 (1.24–1.31)  | < 0.0001 | 1.25 (1.22–1.29)       | < 0.0001 |
| **UTI**                           |                       |                  |                   |          |                        |          |
| Reference                         | 5 452 470             | 24 881           | -                 | -        | -                      | -        |
| Psoriasis                         | 905 170               | 5114             | 1.24 (1.20–1.28)  | < 0.0001 | 1.23 (1.19–1.26)       | < 0.0001 |
| **Gynaecological infections**    |                       |                  |                   |          |                        |          |
| Reference                         | 2 730 940             | 1202             | -                 | -        | -                      | -        |
| Psoriasis                         | 455 790               | 246              | 1.23 (1.07–1.41)  | 0.004    | 1.20 (1.04–1.37)       | 0.01     |
| **Musculoskeletal infections**   |                       |                  |                   |          |                        |          |
| Reference                         | 5 533 190             | 3095             | -                 | -        | -                      | -        |
| Psoriasis                         | 920 980               | 764              | 1.48 (1.37–1.61)  | < 0.0001 | 1.42 (1.31–1.54)       | < 0.0001 |
| **Skin and subcutaneous infections** |                    |                  |                   |          |                        |          |
| Reference                         | 5 442 850             | 18 352           | -                 | -        | -                      | -        |
| Psoriasis                         | 897 730               | 4515             | 1.49 (1.44–1.54)  | < 0.0001 | 1.45 (1.41–1.50)       | < 0.0001 |
| **Opportunistic infections**     |                       |                  |                   |          |                        |          |
| Reference                         | 5 531 270             | 4807             | -                 | -        | -                      | -        |
| Psoriasis                         | 920 870               | 1062             | 1.33 (1.24–1.42)  | < 0.0001 | 1.30 (1.21–1.38)       | < 0.0001 |
| **Other infections**             |                       |                  |                   |          |                        |          |
| Reference                         | 5 498 270             | 15 428           | -                 | -        | -                      | -        |
| Psoriasis                         | 912 930               | 3486             | 1.37 (1.32–1.42)  | < 0.0001 | 1.34 (1.29–1.39)       | < 0.0001 |
| **Sepsis**                       |                       |                  |                   |          |                        |          |
| Reference                         | 5 519 210             | 13 287           | -                 | -        | -                      | -        |
| Psoriasis                         | 917 420               | 3077             | 1.39 (1.34–1.45)  | < 0.0001 | 1.35 (1.29–1.40)       | < 0.0001 |
| **Rare**                          |                       |                  |                   |          |                        |          |
| Reference                         | 5 540 140             | 1761             | -                 | -        | -                      | -        |
| Psoriasis                         | 922 800               | 396              | 1.35 (1.21–1.51)  | < 0.0001 | 1.34 (1.20–1.50)       | < 0.0001 |
| **HIV**                           |                       |                  |                   |          |                        |          |
| Reference                         | 5 549 580             | 214              | -                 | -        | -                      | -        |
| Psoriasis                         | 924 980               | 55               | 1.54 (1.14–2.07)  | 0.0044   | 1.58 (1.17–2.13)       | 0.0025   |
| **Hepatitis**                     |                       |                  |                   |          |                        |          |
| Reference                         | 5 543 860             | 1177             | -                 | -        | -                      | -        |
| Psoriasis                         | 923 550               | 276              | 1.41 (1.23–1.60)  | < 0.0001 | 1.39 (1.22–1.59)       | < 0.0001 |
| **Tuberculosis**                  |                       |                  |                   |          |                        |          |
| Reference                         | 5 549 360             | 391              | -                 | -        | -                      | -        |
| Psoriasis                         | 925 030               | 69               | 1.06 (0.82–1.37)  | 0.66     | 1.05 (0.81–1.36)       | 0.72     |

CI, confidence interval; CNS, central nervous system; GI, gastrointestinal; HR, hazard ratio; URTI, upper respiratory tract infections; UTI, urinary tract infections. *Adjusted for sex, age, ethnicity, socioeconomic status, alcohol-related conditions and Charlson Comorbidity Index.

© 2022 The Authors. British Journal of Dermatology published by John Wiley & Sons Ltd on behalf of British Association of Dermatologists.
Figure 1 Hazard ratios (adjusted for sex, age, ethnicity, socioeconomic status, alcohol-related conditions and Charlson Comorbidity Index) for infections in patients with any psoriasis, patients with mild psoriasis and patients with severe psoriasis compared with the general population. CNS, central nervous system; GI, gastrointestinal; URTI, upper respiratory tract infections.
Infections showed the highest IRs (Table 2). The HR for any severe infections for patients with psoriasis compared with the control group was 1.31 (95% CI 1.29 to 1.32) and the aHR was 1.29 (95% CI 1.27 to 1.31) (Table 3). Psoriasis was associated with the development of all the assessed infections, compared with the control group (Figure 1). The highest observed HR was seen for musculoskeletal, skin and subcutaneous tissue infections (aHR 1.42, 95% CI 1.31 to 1.54 and aHR 1.45, 95% CI 1.41 to 1.50, respectively). The HR for central nervous system infections was 1.39 (95% CI 1.22 to 1.59) and the HR for opportunistic infections was 1.33 (95% CI 1.24 to 1.42). When infections were limited to only those infections leading to hospitalization, it resulted in an IR of 2001 (95% CI 1969.7 to 2034.3) among patients with psoriasis, compared with 1529 (95% CI 1518.5 to 1540.9) among the control group (Table 4), with similar HRs for all severe infections (Figure 2 and Table S3; see Supporting Information).

### Patients with mild psoriasis

The IR among patients with mild psoriasis (IR 2979.1, 95% CI 2939.0 to 3018.8) was higher than the IR in the control group (Table S4), and the HR for patients with mild psoriasis compared with the matched general population was 1.26 (95% CI 1.24 to 1.28) (Table S5). When infections were limited to only those infections leading to hospitalization, it resulted in an IR of 1922.3 (95% CI 1899.5 to 1955.6) among patients with mild psoriasis, with similar HRs for infections overall (Table S6).

### Patients with severe psoriasis

The IR of any severe infections among patients with severe psoriasis (IR 3824.6, 95% CI 3731.6 to 3919.9) was higher than that of the control group (Table 5) and the aHR for patients with severe psoriasis compared with the matched general population was 1.58 (95% CI 1.54 to 1.63) (Figure 1 and Table S7). For any severe infections leading to hospitalization (inpatients only) the IR was higher at 2537.7 (95% CI 2458.8 to 2619.2) among patients with severe psoriasis compared with 1460.9 (95% CI 1437.4 to 1484.7) among the control group (Table S8).

### Incidence rates of any rare infections

#### Patients with any psoriasis

Among patients with any psoriasis, the IR of any rare infections was higher at 42.91 (95% CI 38.89 to 47.35), compared with 31.79 (95% CI 30.34 to 33.31) for the control group (Table 2). The IR was 5.95 (95% CI 4.57 to 7.74) for HIV, 7.46 (95% CI 5.89 to 9.44) for TB, and 29.89 (95% CI 26.56 to 33.63) for hepatitis (Table 2). Psoriasis was associated with an increased risk of any rare infections (aHR 1.34, 95% CI 1.20 to 1.50), which was attributed to higher incidences of HIV and hepatitis but not TB (Table 3). For any rare infections leading to hospitalization (inpatients only), the IR was higher at 8.47 (95% CI 6.78 to 10.57) among patients with psoriasis compared with 6.47 (95% CI 5.83 to 7.18).

| IR per 100 000 person-years among the general population (95% CI) | IR per 100 000 person-years among patients with any psoriasis (95% CI) | IR differences per 100 000 person-years (95% CI) |
|---|---|---|
| Any infections (rare or severe) | 1531.8 (1520.6–1543.0) | 2005.1 (1973.0–2037.7) | 473.3 (452.4–494.7) |
| Serious infections | 341.8 (339.6–344.0) | 460.8 (449.8–471.9) | 119.0 (110.0–128.0) |
| Any severe infections | 1529.7 (1518.5–1540.9) | 2001.8 (1969.7–2034.3) | 472.1 (451.2–493.4) |
| CNS infections | 17.32 (16.25–18.45) | 22.95 (20.06–24.26) | 5.64 (3.81–7.81) |
| URTI | 27.01 (25.67–28.42) | 35.99 (32.92–40.11) | 8.98 (6.63–11.69) |
| Pulmonary infections | 620.59 (613.94–627.31) | 780.45 (762.20–799.15) | 159.9 (148.3–171.8) |
| Heart infections | 29.04 (27.66–30.50) | 36.62 (32.92–40.74) | 7.58 (5.26–10.24) |
| GI infections | 354.08 (349.05–359.18) | 450.42 (436.57–464.72) | 96.34 (87.52–105.5) |
| UTI | 297.49 (292.91–302.13) | 379.82 (367.25–392.83) | 82.33 (74.34–90.70) |
| Gynaecological infections | 23.13 (21.39–25.01) | 27.03 (22.65–32.26) | 3.90 (1.26–7.25) |
| Musculoskeletal infections | 27.58 (26.23–29.00) | 43.11 (39.04–47.57) | 15.53 (12.84–18.57) |
| Skin and subcutaneous tissue infections | 107.76 (105.01–110.57) | 170.76 (162.34–179.63) | 63.00 (57.33–69.06) |
| Opportunistic infections | 46.34 (44.58–48.17) | 63.25 (58.30–68.61) | 16.91 (13.73–20.44) |
| Other infections | 140.97 (137.85–144.16) | 193.81 (184.92–203.13) | 52.84 (47.07–58.97) |
| Sepsis | 218.98 (215.11–222.93) | 302.6 (291.53–314.08) | 83.62 (76.42–91.15) |
| Rare infections | | | |
| HIV | 6.47 (5.83–7.18) | 8.47 (7.68–10.57) | 2.00 (0.95–3.39) |
| Hepatitis | 0.85 (0.64–1.13) | 0.97 (0.51–1.87) | 0.13 (–0.13–0.74) |
| Tuberculosis | 2.74 (2.34–3.22) | 4.34 (3.18–5.91) | 1.59 (0.84–2.69) |
| | 3.01 (2.59–3.50) | 3.35 (2.36–4.77) | 0.34 (–0.23–1.26) |

CI, confidence interval; CNS, central nervous system; GI, gastrointestinal; IR, incidence rate; URTI, upper respiratory tract infections; UTI, urinary tract infections.
Figure 2 Hazard ratios (adjusted for sex, age, ethnicity, socioeconomic status, alcohol-related conditions and Charlson Comorbidity Index) for infections leading to hospitalization (inpatients only) in patients with any psoriasis, patients with mild psoriasis and patients with severe psoriasis compared with the general population. CNS, central nervous system; GI, gastrointestinal; URTI, upper respiratory tract infections.
among the control group (Table 4). Only the association for hepatitis remained significant when infections were limited to those leading to hospitalization (Figure 2 and Table S3).

Patients with mild psoriasis

The IR among patients with mild psoriasis (IR 42.30, 95% CI 38.13 to 46.93) was higher than that found in the control group (Table S4); the HR was also higher than that found in the control group (Table S5). Restricting the definition of infections to only those leading to hospitalization resulted in an IR of 7.86 (95% CI 6.17 to 10.00) among patients with mild psoriasis.

Patients with severe psoriasis

The IR of any rare infections among patients with severe psoriasis (IR 55.69, 95% CI 46.31 to 66.97) was higher than that of the control group (Table 5) and the aHR for patients with severe psoriasis compared with the matched general population was 1.64 (95% CI 1.33 to 2.03) (Figure 1 and Table S7). In particular, the IR of TB was higher among patients with severe psoriasis (Table S8) and an association between TB and severe psoriasis was observed (Figure 1 and Table S9; see Supporting Information). For any severe infections leading to hospitalization (inpatients only), the IR was 12.84 (95% CI 8.74–18.86) among patients with severe psoriasis (Table S8). The association for TB remained significant for patients with severe psoriasis when the definition of infections was restricted to only those leading to hospitalization (Figure 2 and Table S9).

### Discussion

This Danish nationwide population-based cohort study revealed an increased incidence of severe and rare infections among patients with severe and mild psoriasis compared with the general population. The risk was higher for patients with severe psoriasis compared with those with mild psoriasis. To date, this is the first study to report the IRs of severe infections, rare infections and infections leading to hospitalization for patients with psoriasis in Denmark.

In Denmark, patients with psoriasis initiating biological medications are screened for TB and rare viral infections including HBV, HCV and HIV prior to starting such therapies. The resulting data suggest that among patients with psoriasis overall, there were significantly higher rates of any infection (severe or rare). Patients with severe psoriasis had an increased risk of any rare infections, which was attributed to higher incidences of HIV and hepatitis, but not TB, indicating that susceptibility to infection rates may differ depending on psoriasis disease severity. In this patient group, there were higher rates of infections leading to hospitalization. For any rare infections, the association for hepatitis remained significant when infections were limited to only those leading to hospitalization, which supports a recent systematic review showing that patients with psoriasis have an increased risk of severe infections and rare infections.
prevalence of HVC. The current subanalysis showed a variability of infection risk based on severity of disease; however, this might be a result of the methodology used to screen patients. Similar to the previous findings, the current subanalysis also reported significantly higher rates of any, severe, and rare infections among patients with severe psoriasis. The IR of TB was higher among patients with severe psoriasis and an association between TB and severe psoriasis was observed, most likely owing to screening of TB prior to initiation of biologics. Also, there were higher rates of infections leading to hospitalization in this patient group. For any rare infections, the association for TB remained significant when infections were limited to only those leading to hospitalization.

Factors that may explain the increased risk of infection include the altered immune environment in patients with psoriasis, which involves a network of leucocytes and proinflammatory cytokines in disease pathogenesis. Patients with severe psoriasis are defined by their eligibility for systemic or biological. Therefore, the increased risk may be a consequence of treatment and not the severity of psoriasis. In a nationwide cohort study of 190,694 patients with IBD in France, the risks of serious and opportunistic infections were higher with immunosuppressive regimens.

In contrast, a Dutch study revealed a greater risk for serious infection, independent of treatment, in patients with severe psoriasis. Furthermore, a recently published investigation on 44,239 new users of biologics in France found that the risk of serious infections was higher for new users of adalimumab or infliximab vs. etanercept, whereas the risk of serious infections was not increased for users of secukinumab. Certain treatments for psoriasis may aggravate existing infections and, as population-based studies are limited and the evidence is conflicting, the risk of rare infections in patients with psoriasis needs to be continually explored.

Major limitations of the study include the absence of data describing confounding factors, such as weight, body mass index and smoking status. This study could potentially have been affected by surveillance bias, as the increased risk of TB in those with severe psoriasis may be due to screening for TB in this population rather than due to psoriasis or psoriasis treatments. Also, psoriasis severity indexes such as the Psoriasis Area and Severity Index, were not used in this study; however, the disease severity was based on prescription information. This is in agreement with the recent proposed severity categorization from the IPC.

If clinicians are aware of the increased risk of severe infection in patients with severe psoriasis who are being treated with a systemic agent, the surveillance of these patients could be increased for signs of infection.

Acknowledgments

All authors collaborated on writing the manuscript (with the assistance of a professional medical writer funded by Novartis) and made the decision to submit the manuscript for publication. The authors thank Hayley Furlong and Linda Hasnanali of Novartis Ireland Ltd. for providing medical writing/editorial assistance in accordance with Good Publication Practice guidelines (www.ismpp.org/gpp3).

Data availability statement

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymised to respect the privacy of patients who have participated in the study in line with applicable laws and regulations.

References

1 Parisi R, Symmons DP, Griffiths CEM et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol 2013; 133:377–85.
2 Smith CH, Barker JN. Psoriasis and its management. BMJ 2006; 333:380–4.
3 Johnson-Huang LM, Lowes MA, Krueger JG. Putting together the psoriasis puzzle: an update on developing targeted therapies. Dis Model Mech 2012; 5:423–33.
4 Geale K, Henriksson M, Schnitt-Egenolf M. How is disease severity associated with quality of life in psoriasis patients? Evidence from a longitudinal population-based study in Sweden. Health Qual Life Outcomes 2017; 15:1–9.
5 Fowler JF, Duh MS, Rovba L et al. The impact of psoriasis on health care costs and patient work loss. J Am Acad Dermatol 2008; 59:772–80.
6 Norlin JM, Steen Carlsson K, Persson U et al. Resource use in patients with psoriasis after the introduction of biologics in Sweden. Acta Derm Venereol 2015; 95:156–61.
7 Yu AP, Tang J, Xie J et al. Economic burden of psoriasis compared to the general population and stratified by disease severity. Curr Med Res Opin 2009; 25:2429–38.
8 Loft ND, Vaengebjerg S, Skov L. Cancer risk in patients with psoriasis: should we be paying more attention? Expert Review Clin Immunol 2020; 16:479–92.
9 Egeberg A. Psoriasis and comorbidities. Epidemiological studies. Dan Med J 2016; 63:B5201.
10 Vaengebjerg S, Skov L, Egeberg A, Loft ND. Prevalence, incidence, and risk of cancer in patients with psoriasis and psoriatic arthritis: a systematic review and meta-analysis. JAMA Dermatol 2020; 156:421–9.
11 Radtke MA, Schäfer I, Glaeske G et al. Prevalence and comorbidities in adults with psoriasis compared to atopic eczema. J Eur Acad Dermatol Venereol 2017; 31:151–7.
12 Feldman SR, Hur P, Zhao Y et al. Incidence rates of comorbidities among patients with psoriasis in the United States. Dermatol Online J 2018; 24:13030/q12m15n9y.
13 Feldman SR, Zhao Y, Shi L, Tran MH. Economic and comorbidity burden among patients with moderate-to-severe psoriasis. J Manag Care Spec Pharm 2015; 21:874–88.
14 Yang YW, Keller JJ, Lin HC. Medical comorbidity associated with psoriasis in adults: a population-based study. Br J Dermatol 2011; 165:1037–43.
15 Richard MA, Barnette T, Horreau C et al. Psoriasis, cardiovascular events, cancer risk and alcohol use: evidence-based recommendations.
based on systematic review and expert opinion. J Eur Acad Dermatol Venereol 2013; 27 (Suppl. 3):2–11.

16 Miele L, Vallone S, Cefalo C et al. Prevalence, characteristics and severity of non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. J Hepatol 2009; 51:778–86.

17 Wakkee M, de Vries E, van den Haak P, Nijsen T. Increased risk of infectious disease requiring hospitalization among patients with psoriasis: a population-based cohort. J Am Acad Dermatol 2011; 65:1135–44.

18 Kanada K, Schupp C, Armstrong A. Association between psoriasis and viral infections in the United States: focusing on hepatitis B, hepatitis C and human immunodeficiency virus. J Eur Acad Dermatol Venereol 2013; 27:1312–16.

19 Shalom G, Zisman D, Bitterman H et al. Systemic therapy for psoriasis and the risk of herpes zoster: a 500 000 person-year study. JAMA Dermatol 2015; 151:533–8.

20 Kao L-T, Lee C-Z, Liu S-P et al. Psoriasis and the risk of pneumonia: a population-based study. PLOS ONE 2014; 9:e116077.

21 Yuu ZZN, Parisi R, Lunt M et al. Risk of hospitalization and death due to infection in people with psoriasis: a population-based cohort study using the Clinical Practice Research Datalink. Br J Dermatol 2021; 184:78–86.

22 Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014; 29:541–9.

23 Pottegård A, Schmidt SAJ, Wallach-Kildemoes H et al. Data resource profile: the Danish national prescription registry. Int J Epidemiol 2017; 46:798–81.

24 Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011; 39 (7 Suppl.):38–41.

25 Schmidt M, Schmidt SAJ, Sandegaard JL et al. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015; 7:449–90.

26 Strober B, Ryan C, van de Kerkhof P et al. Recategorization of psoriasis severity: Delphi consensus from the International Psoriasis Council. J Am Acad Dermatol 2020; 82:117–22.

27 Loﬁ ND, Andersen CH, Halling-Overgaard AS et al. Validation of psoriasis diagnoses in the Danish National Patient Register. Acta Dermato Venereol 2019; 99:1037–8.

28 Egeberg A, Andersen YMF. Use of topical calcipotriol for identiﬁcation of patients with psoriasis in administrative healthcare data—a validation study. J Eur Acad Dermatol Venereol 2020; 34:e90–1.

29 Kirchgesner J, Lemaitre M, Carrat F et al. Risk of serious and opportunistic infections associated with treatment of inﬂammatory bowel diseases. Gastroenterology 2018; 155: 337–46.e10.

30 Droitcourt C, Vittrup I, Kerbrat S et al. Risk of systemic infections in adults with atopic dermatitis: a nationwide cohort study. J Am Acad Dermatol 2021; 84:290–99.

31 Liu Y, Cui SN, Duan MY et al. Is there a relationship between psoriasis and hepatitis C? A meta-analysis and bioinformatics investigation. Virology J 2021; 18:135.

32 Penso L, Dray-Spira R, Weill A et al. Association between biologics use and risk of serious infection in patients with psoriasis. JAMA Dermatol 2021; 157:1056–65.

33 García-Doval I, Cohen AD, Cazzaniga S et al. Risk of serious infections, cutaneous bacterial infections, and granulomatous infections in patients with psoriasis treated with anti-tumor necrosis factor agents versus classic therapies: prospective meta-analysis of Psinet registries. J Am Acad Dermatol 2017; 76:299–308.e16.

34 Kalb RE, Fiorentino DF, Lebwohl MG et al. Risk of serious infection with biologic and systemic treatment of psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (POS-LAR). JAMA Dermatol 2015; 151:961–9.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Table S1 Treatments used to identify patients with severe psoriasis.

Table S2 List of severe infections and their corresponding International Classiﬁcation of Diseases 10th revision codes.

Table S3 Infections leading to hospitalization (inpatients only) among the general population and patients with any type of psoriasis.

Table S4 Infections among the general population and patients with mild psoriasis.

Table S5 Infections among the general population and patients with mild psoriasis.

Table S6 Infections leading to hospitalization (inpatients only) among the general population and patients with mild psoriasis.

Table S7 Infections among the general population and patients with severe psoriasis.

Table S8 Infections leading to hospitalization (inpatients only) among the general population and patients with severe psoriasis.

Table S9 Infections leading to hospitalization (inpatients only) among the general population and patients with severe psoriasis.