ORIGINAL ARTICLE

Global Risk of Bacterial Skin Infections and Herpesviridae Infections with Ustekinumab, Secukinumab, and Tumour Necrosis Factor-alpha Inhibitors: Spontaneous Reports of Adverse Drug Reactions from the World Health Organization Pharmacovigilance Center

Linda DAVIDSON[1], Juul M. P. A. VAN DEN REEK[2], Florence VAN HUNSEL[3], Elke M. G. J. DE JONG[2] and Bart Jan KULLBERG[1]
[1]Department of Internal Medicine and Radboudumc Center for Infectious diseases (RCI), [2]Department of Dermatology, Radboud University Medical Center, Nijmegen, and [3]Netherlands Pharmacovigilance Centre Lareb, 's Hertogenbosch, The Netherlands

Genetic defects in interleukin-12/23/17 immunity are associated with an increased risk of *Staphylococcus aureus* and herpesvirus skin infections. This study analysed spontaneous safety reports from the WHO Pharmacovigilance Center of bacterial skin or herpesvirus infections associated with secukinumab, ustekinumab and tumour necrosis factor-α inhibitors. Associations found in disproportionality analyses were expressed as reporting odds ratios (ROR). For bacterial skin infections, ustekinumab showed the strongest association (ROR 6.09; 95% confidence interval (95% CI) 5.44–6.81), and, among the tumour necrosis factor-α inhibitors, infliximab showed the strongest association (ROR 4.18; 95% CI 3.97–4.40). Risk was comparable between infliximab and secukinumab (ROR 3.51; 95% CI 3.00–4.09). Secukinumab showed the strongest association with herpes simplex infection (ROR 4.80; 95% CI 3.78–6.10). All biologics were equally associated with herpes zoster. Infliximab was the only biologic associated with cytomegalovirus infection (ROR 5.66; 95% CI 5.08–6.31) and had the strongest association with Epstein-Barr virus infection (ROR 6.90; 95% CI 6.03–7.90). All biologics evaluated were positively associated with bacterial skin infections, herpes simplex, and herpes zoster, compared with all other drugs in the WHO database for which individual case safety reports were collected. The possibility of underreporting, reporting bias and difference in causality assessment between countries and reporters must be taken into account when interpreting the results of disproportionality analyses.

Key words: IL-12/23 inhibitors; IL-17 inhibitors; ustekinumab; secukinumab; bacterial skin infection; Herpesviridae infection.

Accepted Dec 14, 2021; Epub ahead of print Jan 28, 2022

Acta Derm Venereol 2022; 102: adv00648.

DOI: 10.2340/actadv.v102.175

Corr: Linda Davidson, Department of Internal Medicine and Radboudumc Center for Infectious diseases (RCI), Radboud University Medical Center, Geert Grooteplein Zuid 10, NL-6525 GA Nijmegen, The Netherlands. E-mail: gil.linda@yahoo.co.uk

SIGNIFICANCE

Secukinumab, ustekinumab, and tumour necrosis factor-α inhibitors are drugs used for the treatment of inflammatory diseases, including psoriasis. Although these drugs are highly efficient in reducing inflammation, they are also likely to induce risk of infections. To investigate whether these drugs increase the risk of certain bacterial skin and virus infections, spontaneous reports on adverse drug reactions from around the world, collected by the World Health Organization, were analysed. All biologics evaluated were positively associated with bacterial skin infections, herpes simplex, and herpes zoster. Ustekinumab, secukinumab and infliximab increased the risk of bacterial skin and herpes virus infections the most. Clinicians must be vigilant for these infections in patients being treated with secukinumab, ustekinumab, or infliximab.

Staphylococcus aureus and *Streptococcus pyogenes* skin infections are common in the general population, and are facilitated by disruption of the epithelial barrier function (1). The majority of the world population will be infected with (multiple) *Herpesviridae* in their lifetime. After primary infection, these viruses remain in the human body in a latent form (2). Most types of *Herpesviridae*, such as Epstein-Barr virus (EBV) or cytomegalovirus (CMV), as well as herpes simplex, cause primary infections in immunocompetent patients early in life. Although herpes zoster may occur in immunocompetent elderly people, it is more common and often more severe in immunocompromised patients (3, 4). In the immunocompromised host, reactivation of a latent herpes virus causes secondary infection which often recurs as severe and disseminated disease (2, 4, 5).

Genetic defects in interleukin (IL)-12, IL-23, and IL-17 immunity may be associated with *Herpesviridae* and *S. aureus* skin infections, as seen in patients with gain-of-function STAT1 mutations (6–11). Of these patients, 74% develop *S. aureus* skin infections and 38% develop *Herpesviridae* skin infections (6, 7). Inhibitors of IL-17 and IL-12/23 are relatively new treatments for inflammatory disorders. Both ustekinumab and secukinumab are approved for the treatment of moderate-to-severe plaque psoriasis and active psoriatic arthritis. In addition, ustekinumab has been licensed as therapy for moderate-to-severe Crohn's disease and ulcerative colitis, and secukinumab for ankylosing spondylitis (12).

For ustekinumab, multiple cases of bacterial skin infections and *Herpesviridae* infections have been described in clinical trials and case reports (13–15). *Herpesviridae* infections were seen more frequently during the first 12 weeks of treatment with secukinumab compared with etanercept (16). To evaluate the risk of bacterial skin infections and *Herpesviridae* infections during IL-17 and IL-12/23 inhibitors post-authorization, a disproportionality analysis was conducted, based on individual case safety reports (ICSR) from around the world, collected by the WHO Pharmacovigilance Center. A similar analysis was conducted for tumour necrosis factor-α (TNF-α) inhibitors, to put the risk for IL-17 and IL-12/23 inhibitors into perspective for other available biologics.

MATERIALS AND METHODS

The WHO receives spontaneous reports on adverse drug reactions in real-life practice from national Pharmacovigilance Centers worldwide. ICSR contain information on patient characteristics, suspected drug, indication for suspected drug, concomitant drugs, reported reactions and a causality assessment. Reports can be submitted by patients, physicians, pharmacists, and pharmaceutical companies. These reports are archived in VigiBase, the global database of ICSR (17, 18).

ICSR with a Medical Dictionary for Regulatory Activities (MedDRA) term indicative of a *S. aureus* or *S. pyogenes* skin infection or *Herpesviridae* infection in combination with a WHO-Drug term codifying for secukinumab, ustekinumab, etanercept, adalimumab or infliximab, listed as the suspected drug by the reporter, that were present in VigiBase on 2 January 2018 (19, 20) were extracted. There are 5 levels to the MedDRA hierarchy, arranged from very specific to very general. MedDRA preferred terms (PT) included for *S. aureus* or *S. pyogenes* skin infections were cellulitis, erysipelas, folliculitis, furuncle and impetigo. A PT is defined as a single medical concept. Most ICSR do not contain data on the causative pathogen of an infection. Since patients with genetic defects in interleukin (IL)-12, IL-23, and IL-17 immunity are at increased risk of *S. aureus* skin infections, the aim of the current study was to include all reports on bacterial skin infections most likely caused by *S. aureus*. Since the clinical presentations of erysipelas and cellulitis may overlap, these terms are often used interchangeably. Therefore, both terms were included as possible *S. aureus* skin infections, even though erysipelas may be caused by *S. pyogenes*. For *Herpesviridae* infections, all PT indicative of a herpes simplex or herpes zoster infection were combined in the respective category. All ICSR containing a *Herpesviridae* PT not specifying the virus type (simplex or zoster) were categorized into an unclassified category. Included MedDRA PT of herpes simplex and zoster infections are listed in Table SI. EBV and CMV are so-called high-level terms (HLT) in which related PT are already grouped together by MedDRA based on anatomy, pathology, physiology, aetiology or function. Since post-authorization exposure was very limited for ixekizumab, brodalumab, guselkumab, tildrakizumab, and risankizumab, these were not included.

Associations between biologics and bacterial skin infection or *Herpesviridae* infection were calculated and expressed as reporting odds ratios (ROR) with a 95% confidence interval (95% CI). The odds of an event occurring is defined as the likelihood that an event will occur, expressed as a proportion of the likelihood that any other event in the WHO database will occur (see Appendix S1 for further explanation). The ROR represents the odds that an event will occur during treatment with a specified biologic, compared with the odds of the event occurring during treatment with any other drug in the WHO database for which ICSR were collected. An association is defined as a ROR >1 given a minimum of 3 ICSR and the lower limit of the 95% confidence interval (95% CI) >1.

Table I. Association between biologics (all indications) and bacterial skin or *Herpesviridae* infections expressed as reporting odds ratios

Reference group for all indications	Risk relative to full database ($n = 16,343,451$)[a]				
	Th-17 inhibitors ($n = 33,166$)		Tumour necrosis factor-α inhibitors ($n = 896,709$)		
	IL-12/23 inhibitor	IL-17 inhibitors			
Index group Biologics for all indications	Ustekinumab ($n = 17,398$)	Secukinumab ($n = 15,768$)	Etanercept ($n = 403,764$)	Infliximab ($n = 127,623$)	Adalimumab ($n = 365,322$)
Infections	*n* ROR (95% CI)[b]	*n* ROR (95% CI)	*n* ROR (95% CI)	*n* ROR (95% CI)	*n* ROR (95% CI)
Bacterial skin infections[c]	309 6.09 (5.44–6.81)	163 3.51 (3.00–4.09)	3,103 2.70 (2.61–2.80)	1,535 4.18 (3.97–4.40)	2,772 2.65 (2.55–2.76)
Cellulitis[d]	256 6.32 (5.58–7.15)	87 2.34 (1.89–2.88)	2,248 2.44 (2.34–2.54)	1,219 4.15 (3.92–4.40)	1,746 2.07 (1.97–2.17)
Erysipelas[d]	18 7.56 (4.75–12.03)	17 7.88 (4.89–12.70)	147 2.75 (2.33–3.26)	61 3.54 (2.74–5.46)	150 3.12 (2.64–3.68)
Folliculitis[d]	14 4.55 (2.69–7.70)	27 9.75 (6.67–14.24)	117 1.66 (1.38–2.00)	108 4.92 (4.06–5.96)	216 3.52 (3.07–4.05)
Furuncle[d]	19 4.27 (2.72–6.70)	30 7.47 (5.21–10.70)	565 6.15 (5.63–6.72)	126 3.94 (3.30–4.70)	645 7.95 (7.31–8.65)
Impetigo[d]	6 6.28 (2.81–14.02)	4 4.61 (1.73–12.31)	51 2.36 (1.78–3.13)	38 5.58 (4.03–7.73)	51 2.62 (1.97–3.47)
Herpes simplex infection[c]	36 2.29 (1.65–3.18)	68 4.80 (3.78–6.10)	957 2.74 (2.56–2.92)	275 2.41 (2.14–2.72)	961 3.05 (2.85–3.25)
Herpes zoster infection[c]	153 3.27 (2.79–3.84)	79 1.86 (1.49–2.32)	3,023 2.91 (2.80–3.02)	1,231 3.66 (3.46–3.87)	2,777 2.94 (2.83–3.06)
Cytomegalovirus infection[e]	8 0.94 (0.47–1.88)	5 0.65 (0.27–1.56)	82 0.41 (0.33–0.51)	340 5.66 (5.08–6.31)	129 0.72 (0.60–0.85)
Epstein-Barr virus infection[e]	16 3.51 (2.15–5.74)	6 1.45 (0.65–3.23)	192 1.85 (1.60–2.13)	221 6.90 (6.03–7.90)	212 2.27 (1.98–2.61)
Herpes infection unclassified[f]	10 2.47 (1.33–4.60)	5 1.36 (0.57–3.28)	203 2.23 (1.93–2.56)	126 4.36 (3.65–5.20)	250 3.08 (2.71–3.50)

[a]N indicates the number of individual case safety reports (ICSR) in the WHO database. [b]Reporting odds ratio (ROR) (95% CI) denotes the ROR with its 95% confidence interval. [c]All preferred terms (PT) combined, a PT is defined as a single medical concept. [d]MedDRA term on a PT level. [e]MedDRA terms on a high level term (HLT) level in which related PT are grouped together based upon anatomy, pathology, physiology, aetiology or function. [f]All ICSR not containing a *Herpesviridae* type specifying PT were grouped into an unclassified category.

ROR were stratified for psoriasis as reported indication for the biologic. Patient characteristics were compared between biologics using a Kruskal–Wallis test for non-normally distributed variables and a Pearson χ^2 test for distribution of categorical variables.

RESULTS

At the time of data extraction (2 January 2018), a total of 16,343,451 ICSR were archived in the WHO Vigibase database: 17,398 ICSR for ustekinumab, 15,768 for secukinumab, and 896,709 for TNF-α inhibitors (etanercept, infliximab and adalimumab).

Patient characteristics are reported in Table SII (biologics prescribed for all indications) and Table SIII (biologics prescribed for psoriasis). Associations, expressed as ROR, of biologics with bacterial skin infections or *Herpesviridae* infections are shown in **Table I**.

Bacterial skin infections

All biologics were associated with bacterial skin infections. Ustekinumab showed the strongest association of all biologics with bacterial skin infections (ROR 6.09; 95% CI 5.44, 6.81), and, of the TNF-α inhibitors, infliximab showed the strongest association with bacterial skin infections (ROR 4.18; 95% CI 3.97, 4.40). ROR for secukinumab was equal to that of infliximab (ROR 3.51; 95% CI 3.00, 4.09).

Considering specific types of bacterial skin infection, ustekinumab was strongly associated with cellulitis (ROR 6.32; 95% CI 5.58, 7.15), erysipelas (ROR 7.56; 95% CI 4.75, 12.03) and impetigo (ROR 6.28; 95% CI 2.81, 14.02), and, to a lesser extent, with folliculitis (ROR 4.55; 95% CI 2.69, 7.70) and furunculosis (ROR 4.27; 95% CI 2.72, 6.70). Secukinumab was most strongly associated with erysipelas (ROR 7.88; 95% CI 7.89, 12.70), folliculitis (ROR 9.75; 95% CI 6.67, 12.24) and furunculosis (ROR 7.47; 95% CI 5.21, 10.70), and the ROR for association of secukinumab with cellulitus was 2.34 (95% CI 1.89, 2.88) and for impetigo 4.61 (95% CI 1.73, 12.31). Etanercept showed a strong association only with furunculosis (ROR 6.15; 95% CI 5.63, 6.72), for the other bacterial skin infections ROR ranged from 1.66 to 2.75. For infliximab, associations with specific bacterial skin infections were comparable and moderate, with ROR, ranging from 3.54 to 5.58. The only strong association for adalimumab was with furuncle (ROR 7.95; 95% CI 7.31, 8.65), ROR ranged from 2.07 to 3.52 for the other bacterial skin infections.

Among patients with psoriasis (**Table II**), only ustekinumab (ROR 2.36; 95% CI 2.06, 2.71), secukinumab (ROR 1.44; 95% CI 1.18, 1.76) and infliximab (ROR 2.04; 95% CI 1.63, 2.56) were associated with bacterial skin infection. For specific types of bacterial skin infection, both ustekinumab (ROR 2.89; 95% CI 2.48, 3.38) and infliximab (ROR 2.27; 95% CI 1.76, 2.94) were associated with cellulitis. Ustekinumab (ROR 2.31; 95% CI 1.34, 4.00), secukinumab (ROR 3.16; 95% CI 1.76, 5.65) and infliximab (ROR 4.18; 95% CI 2.18, 8.03) were as-

Table II. Association between biologics (psoriasis) and bacterial skin or *Herpesviridae* infections expressed as reporting odds ratios (ROR)

Reference group for psoriasis only	Risk relative to full database ($n = 170,208$)[a]				
	Th-17 inhibitors ($n = 19,158$)		TNF-α inhibitors ($n = 119,147$)		
	IL-12/23 inhibitor	IL-17 inhibitors			
Index group Biologics for psoriasis only	Ustekinumab ($n = 11,704$)	Secukinumab ($n = 7,454$)	Etanercept ($n = 62,737$)	Infliximab ($n = 4,274$)	Adalimumab ($n = 52,136$)
Infections	*n* ROR (95% CI)[b]	*n* ROR (95% CI)	*n* ROR (95% CI)	*n* ROR (95% CI)	*n* ROR (95% CI)
Bacterial skin infections[c]	241 2.36 (2.06–2.71)	101 1.44 (1.18–1.76)	561 0.89 (0.80–0.99)	81 2.04 (1.63–2.56)	520 1.05 (0.95–1.17)
Cellulitis[d]	197 2.89 (2.48–3.38)	58 1.18 (0.91–1.54)	378 0.86 (0.76–0.98)	62 2.27 (1.76–2.94)	346 1.00 (0.88–1.14)
Erysipelas[d]	15 2.31 (1.34–4.00)	13 3.16 (1.76–5.65)	25 0.55 (0.35–0.86)	10 4.18 (2.18–8.03)	22 0.61 (0.38–0.99)
Folliculitis[d]	13 1.82 (1.02–3.24)	14 3.19 (1.82–5.59)	33 0.73 (0.49–1.10)	2 N/A	34 1.01 (0.68–1.52)
Furuncle[d]	15 0.75 (0.44–1.26)	16 1.29 (0.78–2.14)	126 1.34 (1.06–1.69)	5 0.69 (0.28–1.67)	118 1.58 (1.25–2.00)
Impetigo[d]	4 2.17 (0.75–6.23)	2 N/A	8 0.65 (0.29–1.47)	3 4.48 (1.36–14.81)	7 0.72 (0.31–1.69)
Herpes simplex infection[c]	26 1.28 (0.85–1.91)	35 2.87 (2.02–4.09)	89 0.72 (0.56–0.92)	11 1.47 (0.80–2.68)	106 1.23 (0.97–1.55)
Herpes zoster infection[c]	110 1.86 (1.52–2.27)	35 0.87 (0.62–1.22)	338 1.01 (0.88–1.15)	40 1.78 (1.30–2.45)	290 1.05 (0.92–1.21)
Cytomegalovirus (CMV) infection[e]	6 2.03 (0.86–4.79)	3 1.52 (0.47–4.91)	9 0.42 (0.20–0.86)	6 5.83 (2.47–13.76)	10 0.63 (0.31–1.27)
Epstein-Barr virus (EBV) infection[e]	12 1.94 (1.06–3.55)	1 N/A	39 1.17 (0.78–1.76)	6 2.59 (1.13–5.92)	22 0.67 (0.42–1.08)
Herpes infection unclassified[f]	4 0.79 (0.29–2.15)	1 N/A	24 0.84 (0.51–1.37)	2 N/A	29 1.49 (0.93–2.39)

[a]N indicates the number of individual case safety reports (ICSR) in the WHO database. [b]ROR (95% CI) denotes the reporting odds ratio with its 95% confidence interval. [c]All preferred terms (PT) combined, a PT is defined as a single medical concept. [d]MedDRA term on a PT level. [e]MedDRA terms on a high level term (HLT) level in which related PT are grouped together based upon anatomy, pathology, physiology, aetiology or function. [f]All ICSR not containing a *Herpesviridae* type specifying PT were grouped into an unclassified category.

sociated with erysipelas. Ustekinumab (ROR 1.82; 95% CI 1.02, 3.24) and secukinumab (ROR 3.19; 95% CI 1.82, 5.59) were associated with folliculitis. Only etanercept (ROR 1.34; 95% CI 1.06, 1.69) and adalimumab (ROR 1.58; 95% CI 1.25, 2.00) were associated with furuncle. Only infliximab was associated with impetigo (ROR 4.48; 95% CI 1.36, 17.81).

Latency time was defined as the time between starting a drug and occurrence of an adverse drug reaction. For bacterial skin infections, the median latency time was 99 days for ustekinumab, 87 days for secukinumab, 295 days for etanercept, 212 days for adalimumab, and 271 days for infliximab. No comparison between biologics can be made, since follow-up time for ustekinumab, and especially secukinumab, is much shorter than for TNF-α inhibitors. ICSR of TNF-α inhibitors had a higher percentage of females (ustekinumab 46.3%; secukinumab 51.3% vs TNF-α 59.8–71.9%) and reported concomitant immunosuppressive medication more often (ustekinumab 17.8%; secukinumab 10.8% vs TNF-α 24.2–38.3). Only 4.3–15.5% of TNF-α inhibitors were prescribed for psoriasis, compared with 73% for ustekinumab and 55% for secukinumab. Sex distribution and concomitant immunosuppressant use were more comparable between biologics prescribed for psoriasis. Only the reported use of concomitant methotrexate differed between biologics, 11.1% of infliximab reports on bacterial skin infections, compared with 4.4–8% for other biologics.

Herpesviridae infections

All biologics were associated with herpes simplex and herpes zoster infections. Ustekinumab and etanercept were equally associated with herpes simplex and herpes zoster infections. Secukinumab and adalimumab were associated more with herpes simplex than with herpes zoster infections. Infliximab was associated more strongly with herpes zoster than with herpes simplex infections. Of all biologics, secukinumab showed the strongest association with herpes simplex infections (ROR 4.80; 95% CI 3.78, 6.10), ROR for the other biologics were within the same range. Associations with herpes zoster infections were comparable between biologics, except for secukinumab, which had a weaker association. Infliximab was the only biologic associated with cytomegalovirus infections (ROR 5.66; 95% CI 5.08, 6.31) and had the strongest association with Epstein-Barr virus infections (ROR 6.90; 95% CI 6.03, 7.90). Secukinumab was the only biologic not associated with Epstein-Barr virus infections, ROR for ustekinumab (3.51; 95% CI 2.15, 5.74) was higher than for etanercept (1.85; 95% CI 1.60, 2.13) and equal to adalimumab (2.27; 95% CI 1.98, 2.61).

For patients with psoriasis, only secukinumab was associated with herpes simplex infections (ROR 2.87; 95% CI 2.02, 4.09), and only ustekinumab (ROR 1.86; 95% CI 1.52, 2.27) and infliximab (ROR 1.78; 95% CI 1.30, 2.45) were associated with herpes zoster infection. Infliximab was the only biologic associated with cytomegalovirus infection (ROR 5.83; 95% CI 2.47, 13.76). Ustekinumab (ROR 1.94; 95% CI 1.06, 3.55) and infliximab (ROR 2.59; 95% CI 1.13, 5.92) showed an equal association with Epstein-Barr virus infection.

For *Herpesviridae* infections, the median latency time was 155 days for ustekinumab, 71 days for secukinumab, 313 days for etanercept, 211 days for adalimumab, and 117 days for infliximab. Comparable to bacterial skin infections, ICSR of TNF-α inhibitors reported concomitant immunosuppressive medication more often (ustekinumab 13.2%; secukinumab 7.4% vs TNF-α 24–45.1%) and were less often prescribed for psoriasis (ustekinumab 65.9%; secukinumab 40.1% vs TNF-α 1.9–8.4%) compared with ustekinumab and secukinumab. Again, in patients with psoriasis only reports of infliximab reported a higher use of concomitant methotrexate, 22% compared with 3.1–4.8% for other biologics.

DISCUSSION

This study shows that both ustekinumab and secukinumab, as well as TNF-α inhibitors, were associated with an increased risk of bacterial skin and *Herpesviridae* infections, as reported in the global WHO database of individual case safety reports. Ustekinumab, however, showed the strongest association of all biologics with bacterial skin infections (ROR 6.09). Of the TNF-α inhibitors, infliximab showed the strongest association (ROR 4.18) with bacterial skin infections, and the risk was comparable to that of secukinumab (ROR 3.51). For *Herpesviridae* infections, secukinumab had the strongest association of all biologics with herpes simplex infections (ROR 4.80), and risk for other biologics was equal (ROR ranging from 2.29 to 3.05). Risk of herpes zoster infection was comparable and moderate among biologics (ROR ranging from 1.86 to 3.66). Interestingly, only infliximab was associated with cytomegalovirus infections (ROR 5.66) and showed the strongest association with Epstein-Barr virus infections (ROR 6.90) of all biologics. For both bacterial skin infections and *Herpesviridae* infections, individual case safety reports describe that in 24–37% of cases the biologic was withdrawn.

Among patients with psoriasis, ustekinumab (ROR 2.36), secukinumab (ROR 1.44) and infliximab (ROR 2.04) were the only biologics associated with bacterial skin infections. Secukinumab was the only biologic associated with herpes simplex infections (ROR 2.87). Only ustekinumab (ROR 1.86) and infliximab (ROR 1.78) were associated with herpes zoster infections. Again, only infliximab was associated with cytomegalovirus infections (ROR 5.83). Both ustekinumab (ROR 1.94) and infliximab (ROR 2.59) showed a moderate association with Epstein-Barr virus infection.

Both ustekinumab and secukinumab treatment increase the risk of bacterial skin infections and *Herpesviridae* infections compared with all other drugs in the WHO database. Risk of bacterial skin infection of these drugs was higher than the risk of *Herpesviridae* infection, comparable to what was observed in patients with inherited impaired IL-17 and IL-12/23 immunity through STAT1 gain of function mutations (6, 7). Secukinumab is a direct blocker of IL-17 activity. Ustekinumab, on the other hand, binds to a shared subunit of IL-12 and IL-23 thereby inhibiting the T-helper (Th)1 and Th17 pathways and their consecutive IFN-γ and IL-17 production. IFN-γ is crucial in host defence against viruses and plays some role against staphylococcal skin infections (21, 22). IL-17 provides protective immunity against *S. aureus* skin infections by driving neutrophil influx (21, 23, 24). Patients with autosomal hyper-IgE syndrome, in which IL-17 production is absent, develop recurrent *S. aureus* skin and lung infections (25). Moreover, IL-17 seems to be important in preventing recurrence of herpes simplex skin infections (26).

The main strength of this study is the scope of the global WHO database of ICSR, since it collects adverse events from around the world. The conducted disproportionality analyses compare risks of biologics for bacterial skin infection or *Herpesviridae* infection with risks of other drugs in the database as well as for other adverse drug reactions. For additional perspective, associations of ustekinumab and secukinumab were compared with those of TNF-α inhibitors and associations were stratified for prescribing indication with focus on the psoriasis stratum.

Even though spontaneous reporting of adverse drug reactions by physicians, pharmacists, patients and pharmaceutical companies is important to gain insight into post-authorization risks, it also has potential weaknesses. The possibility of under-reporting, reporting bias, and difference in causality assessment between countries and reporters needs to be taken into account when interpreting results of disproportionality analyses. Since most ICSR do not contain data on the causative pathogen of an infection, but only medical diagnoses, it is uncertain whether all reports on presumed *S. aureus* related infections are indeed caused by that pathogen. The medical diagnoses erysipelas (also caused by *S. pyogenes*) and cellulitis (caused by *S. aureus*) are both included in the analyses in order to prevent underestimation of the risk of *S. aureus* skin infections.

In addition, no correction for possible confounders, such as concomitant immunosuppressant medication, was performed. The observed differences in sex distribution and concomitant immunosuppressant use between biologics can be attributed largely to the difference in prescribing indication. Associations were, however, stratified for prescribing indication, making the influence of the underlying disease on infection susceptibility comparable between biologics in the psoriasis stratum. It is notable that the stratum "all indications" contains all indications the specific biologic is approved for, and can therefore differ between biologics. Since patient characteristics, including the use of immunosuppressant medication, of patients with psoriasis were more comparable between biologics, disturbance by these possible confounders was less likely. Associations of secukinumab, ustekinumab and infliximab with bacterial skin infections and *Herpesviridae* infections remained present in the psoriasis stratum. In patients with psoriasis, secukinumab was the only biologic associated with herpes simplex infections and only ustekinumab and infliximab were associated with herpes zoster infections. Interestingly, etanercept and adalimumab had no association with bacterial skin infections and herpes zoster infections in patients with psoriasis. For *Herpesviridae* infections, unfortunately, no categorization of reports into superficial and invasive infections could be made, since most reports mention only the type of herpes virus (simplex, zoster, EBV, CMV) infection and not the location or severity.

To date, clinical trials have not reported an increased risk of bacterial skin infections in secukinumab and ustekinumab users (27, 28). A single case report has described the occurrence of *S. aureus* bacteraemia with iliac artery endarteritis after the third dose of ustekinumab (14). Only a few case reports have been published on bacterial skin infections during TNF-α inhibitor therapy (29, 30). For herpes zoster infections, a large review on IL-17 inhibitors, mainly based on randomized clinical trials, yielded no increased risk of herpes zoster compared with controls (31). In the prospective disease-based registry PSOLAR, hazard ratios for herpes zoster were increased for ustekinumab (2.73; $p=0.054$) and TNF-α inhibitors (2.22; $p=0.116$), although the increases were not significant (32). A retrospective cohort study reported an incidence rate of 5.4 per 100 patient-years (95% CI 0.0–12.6) for ustekinumab, and incidence rates ranged from 0.24 to 0.71 for infliximab, etanercept, and adalimumab (33). A review covering multiple cohort studies, randomized controlled trials and case reports has suggested that infliximab increases the risk of herpes zoster infection, whereas the risk for adalimumab, etanercept and ustekinumab remains controversial (34). Several case reports have described multi-dermatomal herpes zoster infections after initiation of ustekinumab (13). There is not much literature on the risk of herpes simplex infection with Th17 or TNF-α inhibitors. Several case reports, however, have described disseminated Epstein-Barr and cytomegalovirus infections during infliximab therapy (35, 36).

In conclusion, increased risk of bacterial skin infection was most prominent for ustekinumab, secukinumab and infliximab compared with the risk for etanercept and adalimumab. In patients with psoriasis, risk of bacterial skin infection was increased only for ustekinumab, se-

cukinumab and infliximab. For herpes simplex infection, the risk was most prominent for secukinumab compared with the risk for ustekinumab, infliximab, etanercept and adalimumab. Secukinumab was the only biologic associated with herpes simplex infection in patients with psoriasis. Biologics were equally associated with herpes zoster infection. In patients with psoriasis, only ustekinumab and infliximab were associated with herpes zoster infection. For all patients, including the psoriasis subset, risk of cytomegalovirus infection was increased only for infliximab, and infliximab had the strongest association with Epstein-Barr virus infection.

Approval of ustekinumab and secukinumab treatment continues to expand to more indications, and additional IL-23 and IL-17 inhibitors are currently becoming available, thereby increasing the number of patients at risk of bacterial skin infections and *Herpesviridae* infections. Bimekizumab, the newest IL-17 inhibitor, inhibits IL-17F in addition to IL-17A, and led to a much higher incidence of oral candidiasis (15%) in clinical trials, compared with other IL-17 inhibitors (37). It is conceivable that the risk of bacterial skin infections and *Herpesviridae* infections may also be increased with bimekizumab use. Long-term follow-up of spontaneous reports on adverse drug reactions post-authorization helps assess safety risks, thereby assisting clinicians in optimal monitoring of their patients on biologic therapy.

ACKNOWLEDGEMENTS

The authors thank the Uppsala Monitoring Centre, Camilla Westerberg and Tomas Bergvall at the Uppsala Monitoring Centre for their collaboration in this study. The information obtained from VigiBase does not represent the opinion of the WHO or the Uppsala Monitoring Centre.

Funding sources: Radboud University Medical Center.

REFERENCES

1. Triplett KD, Pokhrel S, Castleman MJ, Daly SM, Elmore BO, Joyner JA, et al. GPER activation protects against epithelial barrier disruption by Staphylococcus aureus alpha-toxin. Sci Rep 2019; 9: 1343.
2. Fatahzadeh M, Schwartz RA. Human herpes simplex virus infections: epidemiology, pathogenesis, symptomatology, diagnosis, and management. J Am Acad Dermatol 2007; 57: 737–763; quiz 64–66.
3. Johnson BH, Palmer L, Gatwood J, Lenhart G, Kawai K, Acosta CJ. Annual incidence rates of herpes zoster among an immunocompetent population in the United States. BMC Infect Dis 2015; 15: 502.
4. Ahmed AM, Brantley JS, Madkan V, Mendoza N, Tyring SK. Managing herpes zoster in immunocompromised patients. Herpes 2007; 14: 32–36.
5. Fujisato S, Urushibara T, Kasai H, Ishi D, Inafuku K, Fujinuma Y, et al. A Fatal case of atypical disseminated Herpes zoster in a patient with meningoencephalitis and seizures associated with steroid immunosuppression. Am J Case Rep 2018; 19: 1162–1167.
6. Meesilpavikkai K, Dik WA, Schrijver B, Nagtzaam NM, van Rijswijk A, Driessen GJ, et al. A novel heterozygous mutation in the STAT1 SH2 domain causes chronic mucocutaneous candidiasis, atypically diverse infections, autoimmunity, and impaired cytokine regulation. Front Immunol 2017; 8: 274.
7. Toubiana J, Okada S, Hiller J, Oleastro M, Lagos Gomez M, Aldave Becerra JC, et al. Heterozygous STAT1 gain-of-function mutations underlie an unexpectedly broad clinical phenotype. Blood 2016; 127: 3154–3164.
8. Okada S, Puel A, Casanova JL, Kobayashi M. Chronic mucocutaneous candidiasis disease associated with inborn errors of IL-17 immunity. Clin Transl Immunology 2016; 5: e114.
9. Puel A, Cypowyj S, Bustamante J, Wright JF, Liu L, Lim HK, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. Science 2011; 332: 65–68.
10. Puel A, Cypowyj S, Marodi L, Abel L, Picard C, Casanova JL. Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis. Curr Opin Allergy Clin Immunol 2012; 12: 616–622.
11. Netea MG, Joosten LA, van der Meer JW, Kullberg BJ, van de Veerdonk FL. Immune defence against Candida fungal infections. Nat Rev Immunol 2015; 15: 630–642.
12. Jeon C, Sekhon S, Yan D, Afifi L, Nakamura M, Bhutani T. Monoclonal antibodies inhibiting IL-12, -23, and -17 for the treatment of psoriasis. Hum Vaccin Immunother 2017; 13: 2247–2259.
13. Failla V, Nikkels AF. Ustekinumab and herpes zoster. Dermatology 2011; 222: 119–122.
14. Joost I, Steinfurt J, Meyer PT, Kern WV, Rieg S. Staphylococcus aureus bacteremia with iliac artery endarteritis in a patient receiving ustekinumab. BMC Infect Dis 2016; 16: 586.
15. Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2019; 381: 1201–1214.
16. van de Kerkhof PC, Griffiths CE, Reich K, Leonardi CL, Blauvelt A, Tsai TF, et al. Secukinumab long-term safety experience: a pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis. J Am Acad Dermatol 2016; 75: 83–98.e4.
17. Lindquist M. VigiBase, the WHO Global ICSR database system: basic facts. Drug Informat J 2008; 42: 409–419.
18. World Health Organization. Uppsala Monitoring Center, Vigibase® 2019 [accessed April 12, 2019] Available from: https: //www.who-umc.org/.
19. Medical Dictionary for Regulatory Activities (MedDRA). 2019 [accessed April 12, 2019] Available from: https: //www.meddra.org/.
20. World Health Organization, WHODrug Global. 2019 [accessed April 12, 2019] Available from: https: //www.who-umc.org/whodrug/whodrug-portfolio/whodrug-global/.
21. Cho JS, Pietras EM, Garcia NC, Ramos RI, Farzam DM, Monroe HR, et al. IL-17 is essential for host defense against cutaneous Staphylococcus aureus infection in mice. J Clin Invest 2010; 120: 1762–1773.
22. Kang S, Brown HM, Hwang S. Direct antiviral mechanisms of interferon-gamma. Immune Netw 2018; 18: e33.
23. Archer NK, Adappa ND, Palmer JN, Cohen NA, Harro JM, Lee SK, et al. Interleukin-17A (IL-17A) and IL-17F are critical for antimicrobial peptide production and clearance of staphylococcus aureus nasal colonization. Infect Immun 2016; 84: 3575–3583.
24. Krishna S, Miller LS. Innate and adaptive immune responses against Staphylococcus aureus skin infections. Semin Immunopathol 2012; 34: 261–280.
25. Sastalla I, Williams KW, Anderson ED, Myles IA, Reckhow JD, Espinoza-Moraga M, et al. Molecular typing of staphylococcus aureus isolated from patients with autosomal dominant hyper IgE syndrome. Pathogens 2017; 6: 23.
26. Bagri P, Anipindi VC, Nguyen PV, Vitali D, Stampfli MR, Kaushic C. Novel role for interleukin-17 in enhancing type 1 helper t cell immunity in the female genital tract following mucosal herpes simplex virus 2 vaccination. J Virol 2017; 91: e01234–17.
27. Patel NU, Vera NC, Shealy ER, Wetzel M, Feldman SR. A review of the use of secukinumab for psoriatic arthritis. Rheumatol Ther 2017; 4: 233–246.
28. Ghosh S, Gensler LS, Yang ZJ, Gasink C, Chakravarty SD, Farahi K, et al. Ustekinumab safety in psoriasis, psoriatic

arthritis, and crohn's disease: an integrated analysis of phase ii/iii clinical development programs (vol 42, pg 751, 2019). Drug Safety 2019; 42: 809.
29. Wegscheider BJ, El-Shabrawi L, Weger M, Ardjomand N, Hermann J, Aberer E, et al. Adverse skin reactions to infliximab in the treatment of intraocular inflammation. Eye 2007; 21: 547–549.
30. Lee HH, Song IH, Friedrich M, Gauliard A, Detert J, Rowert J, et al. Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor-alpha antagonists. Brit J Dermatol 2007; 156: 486–491.
31. Wu KK, Lee MP, Lee EB, Wu JJ. Risk of herpes zoster with IL-17 inhibitor therapy for psoriasis and other inflammatory conditions. J Dermatolog Treat 2020; 31: 359–365.
32. Shalom G, Naldi L, Lebwohl M, Nikkels A, de Jong E, Fakharzadeh S, et al. Biological treatment for psoriasis and the risk of herpes zoster: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). J Dermatolog Treat 2019; 30: 534–539.
33. Failla V, Jacques J, Castronovo C, Nikkels AF. Herpes zoster in patients treated with biologicals. Dermatology 2012; 224: 251–256.
34. Adelzadeh L, Jourabchi N, Wu JJ. The risk of herpes zoster during biological therapy for psoriasis and other inflammatory conditions. J Eur Acad Dermatol Venereol 2014; 28: 846–852.
35. Ueda M, Tateishi T, Shigeto H, Yamasaki R, Ohyagi Y, Kira J. [A case of acute disseminated encephalomyelitis associated with Epstein-Barr virus reactivation during infliximab therapy]. Rinsho Shinkeigaku 2010; 50: 461–466 (in Japanese).
36. Helbling D, Breitbach TH, Krause M. Disseminated cytomegalovirus infection in Crohn's disease following anti-tumour necrosis factor therapy. Eur J Gastroenterol Hepatol 2002; 14: 1393–1395.
37. Reich K, Papp KA, Blauvelt A, Langley RG, Armstrong A, Warren RB, et al. Bimekizumab versus ustekinumab for the treatment of moderate to severe plaque psoriasis (BE VIVID): efficacy and safety from a 52-week, multicentre, double-blind, active comparator and placebo controlled phase 3 trial. Lancet 2021; 397: 487–498.