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Conducting a real-world study of Tumor Necrosis factor-alpha inhibitors-induced Systemic Lupus Erythematosus based on the FAERS database

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This study characterized the risk and characteristics of tumor necrosis factor-α (TNF-α) inhibitors-induced systemic lupus erythematosus (SLE) in a mass medication population based on the FAERS database. Using the Standardized MedDRA Query (SMQ), adverse drug reaction (ADR) reports related to SLE of infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol were collected from the FAERS database starting from the data retrieval quarter up to the fourth quarter of 2023. Signal detection was performed using the Reporting Odds Ratio (ROR) method and the Bayesian Confidence Interval Propagation Neural Network (BCPNN) method to comprehensively explore the risks. Subgroup analyses were conducted for different genders and age groups to provide a detailed insight into the risks. A total of 12,080 reports of TNF-α inhibitors-induced SLE have been collected, with over 90% of the reports showing serious outcomes, including life-threatening, death and others. Notably, deaths were prominently associated with certolizumab pegol and etanercept. Regarding time to onset, the median time to onset after drug use was over 7 months for infliximab, adalimumab, and etanercept, while for golimumab and certolizumab pegol, the median time to onset was around 2 months post-treatment. At the SMQ level, all five TNF-α inhibitors showed statistically significant signals in the overall population, with the strength of association ranked as infliximab > adalimumab > certolizumab pegol > golimumab > etanercept. In terms of PT level, apart from signals related to lupus-like syndrome, systemic lupus erythematosus, and systemic lupus erythematosus rash, notable findings include the higher signal intensity of SLE arthritis in the subgroup of male with adalimumab, lupus nephritis risk associated with etanercept in the children (0–14 years) subgroup, and rare and severe occurrences of pericarditis lupus and lupus pleurisy induced by infliximab. This study utilized large-scale real-world data to reveal varying degrees of SLE associated with five TNF-α inhibitors and characterized specific risk signals of concern across gender and age subgroups. This suggests that different TNF-α inhibitors should be continuously monitored for SLE-induced complications in clinical practice, and that appropriate drug management should be carried out for different patients. Further research is necessary to validate our findings.

Keywords Systemic lupus erythematosus, FAERS database, Disproportionality analysis;, Pharmacovigilance

Tumor necrosis factor-alpha (TNF-α), a pleiotropic pro-inflammatory cytokine, is involved in the pathophysiology of various autoimmune diseases[1]. In normal immune responses, TNF-α activates the immune system for immune regulation; however, excessive or aberrant release of TNF-α may trigger autoimmune diseases[2].

Currently, tumor necrosis factor-alpha inhibitors used in clinical practice include infliximab (INF), adalimumab (ADA), etanercept (ETN), golimumab (GOL), and certolizumab pegol (CZB), which are primarily used for rheumatoid arthritis (RA), ankylosing spondylitis (AS), inflammatory bowel disease (IBD), psoriasis (PsO), and other autoimmune diseases in clinical treatment[3].

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Due to the fact that the immune system of the body is in a relatively stable and coordinated state at multiple levels, including holistic, cellular, and molecular levels, treatment with TNF-α inhibitors and other biologics may lead to new immune system dysregulation and adverse drug reactions (ADRs). Common ADRs with TNF-α inhibitors include acute infusion reactions, infections, malignant tumors, and autoimmune reactions[4]. The association between TNF-α inhibitors and systemic lupus erythematosus (SLE) has been confirmed by the disappearance of symptoms after discontinuation of the relevant drug. According to case data from the BIOGEAS registry[5], anti-TNF-α induced lupus erythematosus (ATIL) and lupus-like syndrome were the most common in a registry of autoimmune diseases associated with TNF-α inhibitors, and their occurrence is often accompanied by positive anti-nuclear antibody (ANA) and anti-double stranded DNA antibody (anti-dsDNA)[6,7].

A clinical trial for rheumatoid arthritis found that when infliximab caused SLE, rash symptoms no longer appeared after switching to etanercept, indicating that the induction of ANA and anti-dsDNA by TNF-α inhibitors is attributed to drug-specific characteristics rather than a class effect[8]. Studies have also reported death cases of etanercept-induced lupus nephritis[9], emphasizing the need to consider the risk and safety profiles of inducing SLE during treatment with different TNF-α inhibitors. Although there have been studies using the VigiBase database to identify suspected drugs associated with drug-induced systemic lupus (DIL), such as infliximab and adalimumab[10], there has been no investigation into the specific association between different TNF-α inhibitors and SLE. Furthermore, the limited number of case reports from the literature can only provide some epidemiological evidence and cannot yet al.low for a cross-comparison of risks between different drugs.

Data mining is an important method for the detection of ADR signals in pharmacovigilance studies, and in addition to being used for the early detection of safety signals for new drugs, it is also of great value in the continuous safety monitoring of older drugs[11]. The FDA Adverse Event Reporting System (FAERS) is the primary source of information used by the FDA for post-marketing safety monitoring and evaluation of drugs, and collects reports from healthcare professionals, consumers, and drug manufacturers worldwide, which can provide insights into real-world ADR occurrences to a certain extent[12]. Therefore, this study conducted a disproportionality pharmacovigilance retrospective study based on the FAERS database to characterize the risks of SLE occurrence induced by different TNF-α inhibitors in a mass population, and subgroup analyses by age and gender were performed to fully understand the risk of SLE induced by TNF-α inhibitors in patient populations with different characteristics.

Materials and methods

Data source

In this study, 80 quarters of data were collected from the FAERS database from Q1 2004 to Q4 2023, of which infliximab, adalimumab and etanercept were analyzed from Q1 2004 to Q4 2023, and golimumab and certolizumab pegol were analyzed according to the corresponding data from the quarter of the U.S. market launch (i.e., the data retrieval start quarter) to Q4 2023, respectively. Each quarter's ASCII data contained seven sub-files: describing patient demographics and management information (DEMO), adverse event coding (REAC), drug information (DRUG), patient outcomes (OUTC), reporting sources (PRSR), date of initiation and termination (THER), and diagnoses and indications for drug use (INDI).

Data cleaning

This study imported downloaded ASCII data into SAS 9.4 (Statistics Analysis System Institute Inc.) and performed data cleaning according to the data deduplication rules and the list of reports to be deleted provided in the FDA official instruction document[13]. Firstly, the study linked report information using the unique patient identifier PRIMARYID, selected PRIMARYID, CASEID, and FDA_DT fields from the DEMO table, sorted based on CASEID, FDA_DT, and PRIMARYID, and retained the report with the highest FDA_DT value for reports with the same CASEID; for reports with the same CASEID and FDA_DT, the report with the highest PRIMARYID value was retained. Subsequently, starting in the first quarter of 2019, each quarterly data package contained a list of reports to be deleted. After data deduplication, reports with CASEID listed in the deletion report list were excluded. Reports with missing or low-quality key information such as gender, age, drug, and adverse reaction, as well as those with illogical reporting time sequences, were also removed from the raw data.

Data standardization

For the age, six age units exist in the FDA (DEC - decades, YR - years, MON - months, WK - weeks, DY - days, HR - hours), and uniform standardization of age units was performed to allow for subsequent population grouping.

For the adverse drug reaction, ADR names were standardized using the Preferred Term (PT) from the Medical Dictionary for Regulatory Activities (MedDRA®) version 26.1, and mapped to the System Organ Class (SOC) level to ensure term consistency.

For time to onset, it was determined by the time interval between EVENT_DT (date of Systemic Lupus Erythematosus ADR) and START_DT (date of initiation of treatment with TNF-α inhibitors) in the THER subfile[14] and excluded date inaccuracies, missing dates, and reports in which the start date of drug therapy was after the date of the adverse reaction.

Report query

Selection of drug

eneric and brand names were used to identify adverse drug cases involving TNF-α inhibitors (infliximab, etanercept, adalimumab, certolizumab pegol, or golimumab) (Table 1). TNF-α inhibitors with a reported role coded as "primary suspect" (PS) were evaluated in the primary analysis[14]. Essential information from each

Generic Name	Brand Name	Data retrieval start quarter
Infliximab	Remicade	2004 Q1
Adalimumab	Humira	2004 Q1
Etanercept	Enbrel	2004 Q1
Golimumab	Simponi Aria	2009 Q2
Certolizumab pegol	Cimzia	2008 Q2

Table 1. Generic names, Brand names, and Data retrieval start quarter for five TNF-α inhibitors.

The term of PT	Code	The term of PT	Code
Lupus cystitis	10,074,714	Lupus pancreatitis	10,067,750
Lupus pleurisy	10,073,694	Lupus vasculitis	10,058,143
Acute cutaneous lupus erythematosus	10,057,928	Lupus-like syndrome	10,050,551
Antinuclear antibody positive	10,060,055	Chronic cutaneous lupus erythematosus	10,057,929
Antinuclear antibody increased	10,064,726	Cutaneous lupus erythematosus	10,056,509
Lupus myositis	10,079,642	Neuropsychiatric lupus	10,063,663
Lupus encephalitis	10,025,130	Systemic lupus erythematosus	10,042,945
Lupus nephritis	10,025,140	Systemic lupus erythematosus disease activity index decreased	10,067,658
Lupus myocarditis	10,066,391	Systemic lupus erythematosus disease activity index abnormal	10,067,659
Lupus enteritis	10,067,738	Systemic lupus erythematosus disease activity index increased	10,067,657
Lupus pneumonitis	10,057,481	Systemic lupus erythematosus rash	10,042,946
Peritonitis lupus	10,062,898	SLE arthritis	10,040,968
Lupus hepatitis	10,067,737	Neonatal lupus erythematosus	10,057,887
Pericarditis lupus	10,058,149	Subacute cutaneous lupus erythematosus	10,057,903
Lupus endocarditis	10,058,225	Central nervous system lupus	10,076,328

Table 2. The PT term and code included in the narrow term of Systemic Lupus Erythematosus.

	Target ADR	Other ADRs	Total
Target drugs	A	B	A + B
Other drugs	C	D	C + D
Total	A + C	B + D	n = A + B + C + D

Table 3. Two-by two contingency table for measure of disproportionality.

report was extracted and analyzed, including demographic data (age and sex), administrative information (type of reporter), and ADR data (time to onset and outcome).

Definition of adverse drug reactions

All ADR in FAERS are coded using the PT from the MedDRA, and specific PTs are associated with high-level terms (HLTs), high-level group terms (HLGTs), and system organ classes (SOCs). Additionally, Standardized MedDRA Queries (SMQ) are used, which are widely accepted datasets of PTs related to specific diseases, with narrow terms and broad terms distinguished[15].

To enhance the specificity of the data, this study used a narrow search approach with the standard SMQ from MedDRA 26.1, searching for SMQ code 20,000,045, with the term set defined as systemic lupus erythematosus, containing 30 PTs (Table 2).

Disproportionality analysis

The basic concept of disproportionality analysis is that a signal is considered to be generated if the combined frequency of drug-specific events in the database is significantly higher than the background frequency of the entire database and exceeds the corresponding threshold. It calculates indicators to determine a safety signal based on counts of the target drug, other drugs, target ADRs, and other ADRs, as shown in the following 2×2 columnar table (Table 3).

This study uses the reporting odds ratio method (ROR) in the Frequency counting method and the Bayesian confidence interval propagation neural network method (BCPNN) in the Bayesian method for signal mining. The ROR method is based on the classical four-cell table, which can eliminate a large number of biases and has high sensitivity, while the BCPNN method combines Bayesian logic and neural network structure, which

provides more stable results and higher specificity. The combination of the two methods can reduce the result bias caused by using a single algorithm and reduce the false positive rate[16,17].

Therefore, a positive signal detected by both methods simultaneously was judged as suspicious in this study (Table 4), suggesting that the association between the drug and the target ADR was statistically significant, and that the stronger the signal intensity, the stronger the statistical association between the two[18,19]; and in view of the excellent performance of the ROR method in terms of sensitivity and early detection ability of the signals[20], the results were visualized by using the ROR values and their 95% CIs to plot the correlation graphs for result visualization.

To examine the impact of age and gender on the ADR of TNF-α inhibitors causing systemic lupus erythematosus, subgroup analyses were conducted for age and gender. Age groups were divided into Children (0–14 years), Young adults (15–24 years), Adults (25–65 years), and Elderly (≥66 years)[21]; gender groups were male and female. ADR report records for the corresponding populations were extracted for analysis.

Data statistical analysis and graph plotting were performed using Microsoft Office Excel 2020, Origin 2024, and GraphPad Prism 9.5.0 tools.

Results

Descriptive analysis

During the period from Q1 2004 to Q4 2023, the FAERS database received a total of 20,755,633 reports, and after data cleaning, 17,307,196 valid reports were ultimately retained for signal detection. Of which, 1,373,016 reports were attributed to TNF-α inhibitors, a total of 12,080 reports related to TNF-α inhibitors were reported as "Systemic Lupus Erythematosus" (Table 5).

Among the reports of SLE caused by the 5 TNF-α inhibitors, adalimumab ($n=4569$, 37.82%), infliximab ($n=5058$, 41.87%), and etanercept ($n=1836$, 15.20%) were involved in a higher number of cases compared to other similar products, indicating longer duration of use for these three TNF-α inhibitors.

In terms of gender, female patients accounted for a higher proportion, ranging from 64 to 86%. In terms of age, the majority of patients in the systemic lupus erythematosus ADR caused by the five TNF-α inhibitors were in the Adults (25–65) age group, with a median age distribution between 45 and 52 years. The labeling for golimumab and certolizumab pegol mentions that "safety in children and adolescents under 18 years of age has not been established and is not recommended". Based on the age data collected from the reports, the minimum ages for the use of these two drugs were 22 and 18 years, respectively, indicating no unreasonable use in patients under 18 years old in the real world.

SLE was reported by physicians in 35.54% and 42.70% of reports for infliximab and etanercept, respectively, while SLE was more frequently reported by consumers treated with adalimumab, golimumab, and certolizumab pegol, suggesting that awareness of SLE induced by TNF-α inhibitors is increasing among people other than healthcare professionals.

Over 90% of the reports of SLE caused by the five TNF-α inhibitors were categorized as serious, with the most common outcomes being other serious medical events and hospitalization-initial or prolonged. Furthermore, reports of patient deaths were present for all 5 TNF-α inhibitors, with certolizumab pegol and etanercept having the highest proportion of reports leading to death. The above results contribute to the preliminary understanding of the severity and clinical regression of SLE induced by TNF-α inhibitors, suggesting that patients who develop SLE with TNF-α inhibitors need to be closely monitored during clinical practice and that the risk of developing severe regression is highly emphasized.

Algorithms	Equation	Criteria
ROR	$ROR = AD/BC$ $ROR\ 95\%CI = e^{\ln(ROR)\pm1.96\sqrt{(\frac{1}{A}+\frac{1}{B}+\frac{1}{C}+\frac{1}{D})}}$	A≥3 Lower limit of 95%CI>1
BCPNN	$IC = log_2\frac{A(A+B+C+D)}{(A+B)(A+C)}$ $\gamma=\gamma_{ij}\frac{(N+\alpha)(N+\beta)}{(A+B+\alpha_i)(A+C+\beta_j)}$ $E(IC)=\log_2\frac{(A+\gamma_{ij})(N+\alpha)(N+\beta)}{(N+\gamma)(A+B+\alpha_i)(A+C+\beta_j)}$	A≥3 IC-2SD>0
	$V(IC)=\frac{1}{(log2)^2}\{[\frac{N-A+\gamma-\gamma_{ij}}{(A+\gamma_{ij})(1+N+\gamma)}]+[\frac{N-A-B+\alpha-\alpha_i}{(A+B+\alpha_i)(1+N+\alpha)}]+[\frac{N-A-C+\beta-\beta_j}{(A+B+\beta_i)(1+N+\beta)}]\}$	
	$SD=2\sqrt{V(IC)}$ $IC-2SD=E(IC)-2SD$	

Table 4. Equations and criteria for ROR and BCPNN.
γ, γ_{ij} are the Dicichlet distribution parameter; α_i, α, β_j, β are Beta distribution parameter; SD is the standard deviation; $IC-2SD$ is the lower limit of IC 95% CI; hypothesis $\alpha=\beta=2$, $\gamma_{ij}=\beta_j=\alpha_i=1$

Clinical characteristics	infliximab	adalimumab	etanercept	golimumab	certolizumab pegol
Gender, number (%)					
Male	767 (16.79)	723 (14.29)	214 (11.66)	20 (13.33)	29 (6.21)
Female	2950 (64.57)	4025 (79.58)	1486 (80.94)	113 (75.33)	402 (86.08)
Unspecified	852 (18.65)	310 (6.13)	136 (7.41)	17 (11.33)	36 (7.71)
Age (years), number (%)					
Children (0–14)	39 (0.85)	24 (0.47)	22 (1.20)	0 (0.00)	0 (0.00)
Young adults (15–24)	157 (3.44)	131 (2.59)	52 (2.83)	1 (0.67)	9 (1.93)
Adults (25–65)	1800 (39.40)	2018 (39.90)	945 (51.47)	76 (50.67)	200 (42.83)
Elderly (≥66)	179 (3.92)	250 (4.94)	163 (8.88)	10 (6.67)	25 (5.35)
Unspecified	2394 (52.40)	2635 (52.10)	654 (35.62)	63 (42.00)	233 (49.89)
Age (years) median (IQR, Q1-Q3) [Data availability]	45.00 (35.00,56.00) [2175]	49.00 (39.00,58.00) [2423]	51.00 (42.00,61.00) [1182]	52.00 (43.00,57.00) [87]	46.50 (40.00,58.00) [234]
Age (years) min, max	1.00, 90.00	5.00, 90.00	2.00, 91.00	22.00, 80.00	18.00, 83.00
Reporting sources, number (%)					
Physician	1624 (35.54)	1218 (24.08)	784 (42.70)	42 (28.00)	109 (23.34)
Pharmacist	512 (11.21)	314 (6.21)	204 (11.11)	39 (26.00)	133 (28.48)
Other health-professional	1036 (22.67)	249 (4.92)	276 (15.03)	18 (12.00)	51 (10.92)
Consumer	1349 (29.53)	3193 (63.13)	512 (27.89)	48 (32.00)	164 (35.12)
Lawyer	9 (0.20)	3 (0.06)	3 (0.16)	0 (0)	1 (0.21)
Unspecified	39 (0.85)	81 (1.60)	57 (3.10)	3 (2.00)	9 (1.93)
Seriousness, number (%)					
Serious	4485 (98.16)	4560 (90.15)	1656 (90.20)	144 (96.00)	434 (92.93)
Non-Serious	84 (1.84)	498 (9.85)	180 (9.80)	6 (4.00)	33 (7.07)
Outcome, number (%)					
Death	48 (1.07)	66 (1.45)	42 (2.54)	3 (2.08)	15 (3.46)
Life-Threatening	60 (1.34)	41 (0.90)	33 (1.99)	5 (3.47)	9 (2.07)
Hospitalization-Initial or Prolonged	625 (13.94)	637 (13.97)	260 (15.70)	35 (24.31)	74 (17.05)
Disability	89 (1.98)	60 (1.32)	33 (1.99)	2 (1.39)	18 (4.15)
Congenital Anomaly	0 (0.00)	3 (0.07)	0 (0.00)	0 (0.00)	0 (0.00)
Required Intervention to Prevent Permanent Impairment/Damage	3 (0.07)	12 (0.26)	6 (0.36)	0 (0.00)	0 (0.00)
Other	3660 (81.61)	3741 (82.04)	1282 (77.42)	99 (68.75)	318 (73.27)
Time to onset, days, IQR(Q1-Q3)	250.00 (36.00,749.00)	217.00 (53.00,699.00)	304.00 (53.00,925.00)	79.00 (9.00,255.50)	44.00 (0.00,206.00)
Time to onset, days, min, max	0.00,7395.00	0.00,5428.00	0.00,7642.00	0.00,2150.00	0.00,3134.00

Table 5. Five TNF-α inhibitors-induced systemic lupus erythematosus reports basic information. Note: The outcome was counted on a patient dimension, and if multiple outcomes were documented in a single report, they were ranked in descending order of severity, with only the most severe outcome considered (death > life-threatening > hospitalization-initial or prolonged > disability > congenital anomaly > required intervention to prevent permanent impairment/damage > other)[22,23]. Also, due to missing information indicating incomplete outcome data, the proportion of outcomes occurring in each report was calculated using the outcomes for which data were available as the base.

The median time to onset for infliximab, adalimumab, and etanercept was 250d (IQR 36, 749), 217d (IQR 53, 699), and 304d (IQR 53, 925), SLE occurred more than 7 months after drug administration; the median time to onset for golimumab and certolizumab was 79d (IQR 9, 255.5), and 44d (IQR 0, 206), with SLE occurring approximately 2 months after dosing. Based on the reports with TTO data, further analysis of the time of onset (Fig. 1) showed that the induction of SLE by the five TNF-α inhibitors was mainly concentrated within 90 days after treatment with the drugs, and the possibility of inducing SLE also existed after 720 days post-dose.

Disproportionality analysis at the SMQ level

In the SMQ narrow term set of SLE, all five TNF-α inhibitors showed statistically significant signals (Fig. 2A), with the signal strength ranking as infliximab > adalimumab > certolizumab pegol > golimumab > etanercept, suggesting differences in the risk of SLE induced by different TNF-α inhibitors. Infliximab had the highest risk of inducing SLE, followed by adalimumab, with etanercept presenting the lowest risk.

In order to further investigate individual characteristics, this study conducted subgroup analyses based on gender and age, visualizing them according to their ROR values (Fig. 2B, 2C).

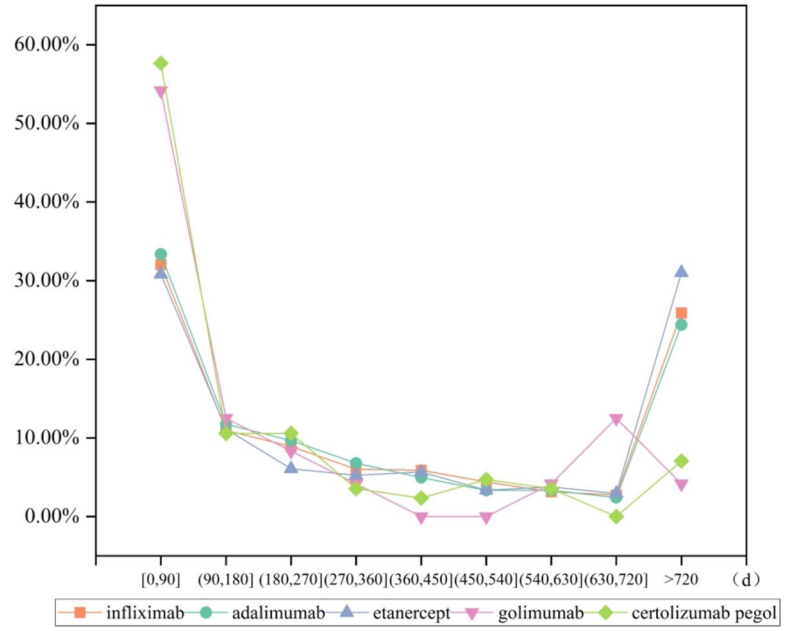


Fig. 1. Time-to-onset analysis of systemic lupus erythematosus induced by five TNF-α inhibitors.

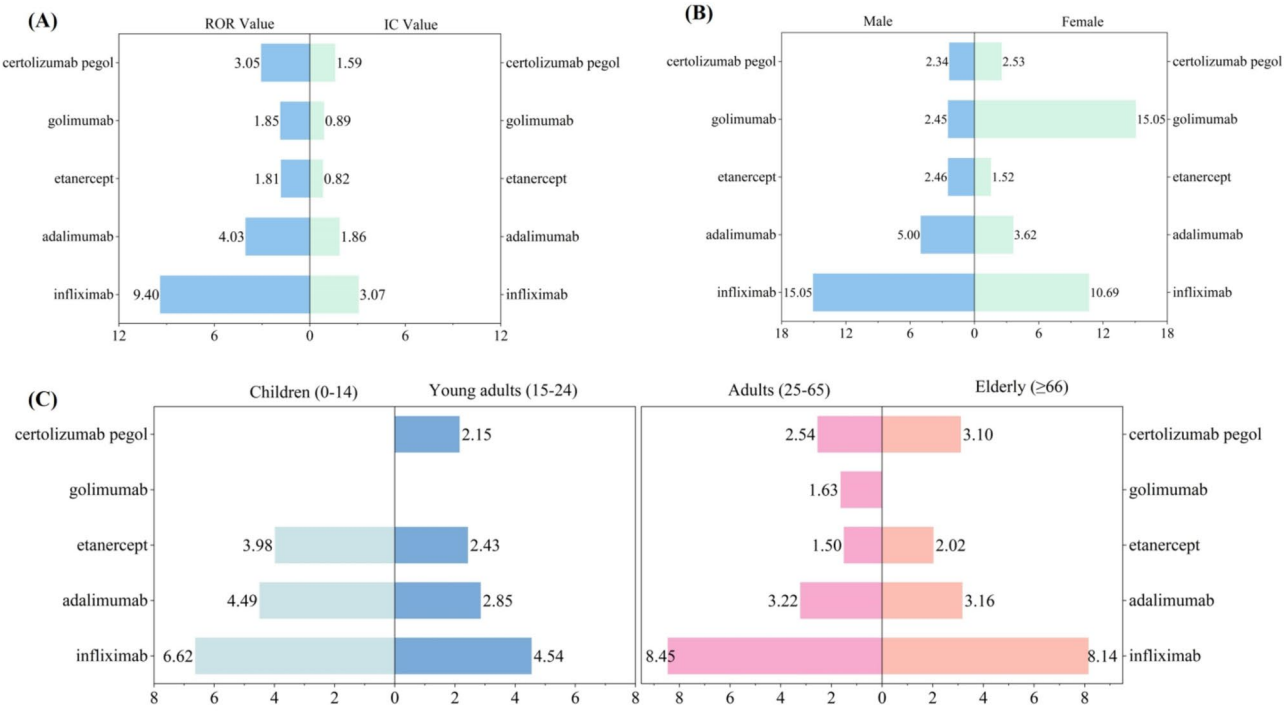


Fig. 2. Disproportionality analysis results of five TNF-α inhibitors-induced systemic lupus erythematosus based on overall population, gender subgroups and age subgroups: (**A**) ROR and IC values of five TNF-α inhibitors-induced SLE in the overall population. (**B**) ROR values of five TNF-α inhibitors-induced SLE in different gender subgroups. (**C**) ROR values of five TNF-α inhibitors-induced SLE in different age subgroups.

In the gender subgroup analysis results (Fig. 2B), all five TNF-α inhibitors showed signals. For the male subgroup, infliximab had the highest risk of inducing SLE ($n = 785$, ROR 15.05, 95% CI 13.95–16.23), while certolizumab pegol had the lowest risk ($n = 29$, ROR 2.34, 95% CI 1.62–3.37); for the female subgroup, golimumab had the highest ROR value for causing systemic lupus erythematosus, at 15.05, with etanercept presenting the lowest risk ($n = 1558$, ROR 1.52, 95% CI 1.45–1.60).

In the four age groups (Fig. 2C), infliximab, adalimumab, and etanercept all showed signals for SLE, with infliximab presenting the highest risk and adalimumab following closely. Golimumab only showed a positive signal in the Adults subgroup ($n = 76$, ROR 1.63, 95% CI 1.30–2.04); except for the Children subgroup, certolizumab pegol showed positive signals in the other three subgroups.

Disproportionality analysis at the PT level

Specifically at the PT level, based on the 30 PTs under the SLE narrow term set, a heat map was drawn according to their ROR values for positive signals detected by both methods (Fig. 3). In the overall population, the number of positive signals generated by infliximab, adalimumab, certolizumab, golimumab, and etanercept were 11, 9, 6, 3, and 3, respectively, and the positive signals generated together were lupus-like syndrome, systemic lupus erythematosus, and systemic lupus erythematosus rash.

Among them, the positive signals of infliximab were mainly focused on lupus-like Syndrome ($n = 2580$, ROR 41.45, 95% CI 39.48–43.50), pericarditis lupus ($n = 5$, ROR 17.98, 95% CI 6.75–47.90), lupus pleurisy ($n = 5$, ROR 13.83, 95% CI 5.31–36.01); ADR with top ROR values for adalimumab were mainly systemic lupus erythematosus disease activity index increased ($n = 6$, ROR 12.29, 95% CI 4.67–32.23) and antinuclear antibodies increased ($n = 161$, ROR 6.08, 95% CI 5.12–7.22); and etanercept was associated with systemic lupus erythematosus rash ($n = 64$, ROR 3.72, 95% CI 2.88–4.81), and cutaneous lupus erythematosus ($n = 116$, ROR 2.67, 95% CI 2.21–3.22); and risk signals for golimumab and certolizumab pegol were mainly concentrated in the 3 PTs of lupus-like syndromes, systemic lupus erythematosus, and systemic lupus erythematosus rash.

Disproportionality analysis of gender subgroups

In the gender subgroup analysis, the positive signals detected by both methods were plotted in a forest plot according to their ROR values and 95% CI (Fig. 4).

In the male subgroup, signals with higher risk were lupus-like syndrome due to infliximab ($n = 428$, ROR 41.05, 95% CI 36.61–46.02), SLE arthritis due to adalimumab ($n = 6$, ROR 20.21, 95% CI 7.19–56.77), and antinuclear antibody increased due to infliximab ($n = 29$, ROR 14.35, 95% CI 9.7–21.24).

In the female subgroup, higher risk signals were lupus-like syndrome with infliximab ($n = 1646$, ROR 52.17, 95% CI 49.13–55.39) and golimumab ($n = 428$, ROR 41.05, 95% CI 36.61–46.02), and pericarditis lupus due to infliximab ($n = 4$, ROR 29.63, 95 95% CI 9.66–90.87).

For the five TNF-α inhibitors, two positive signals, lupus-like syndrome and systemic lupus erythematosus, were jointly detected in both the male and female patient groups. Pericarditis lupus, chronic cutaneous lupus erythematosus, and SLE arthritis were detected in the female group with infliximab compared with the male group; systemic lupus erythematosus disease activity index increased was detected in the female group with the

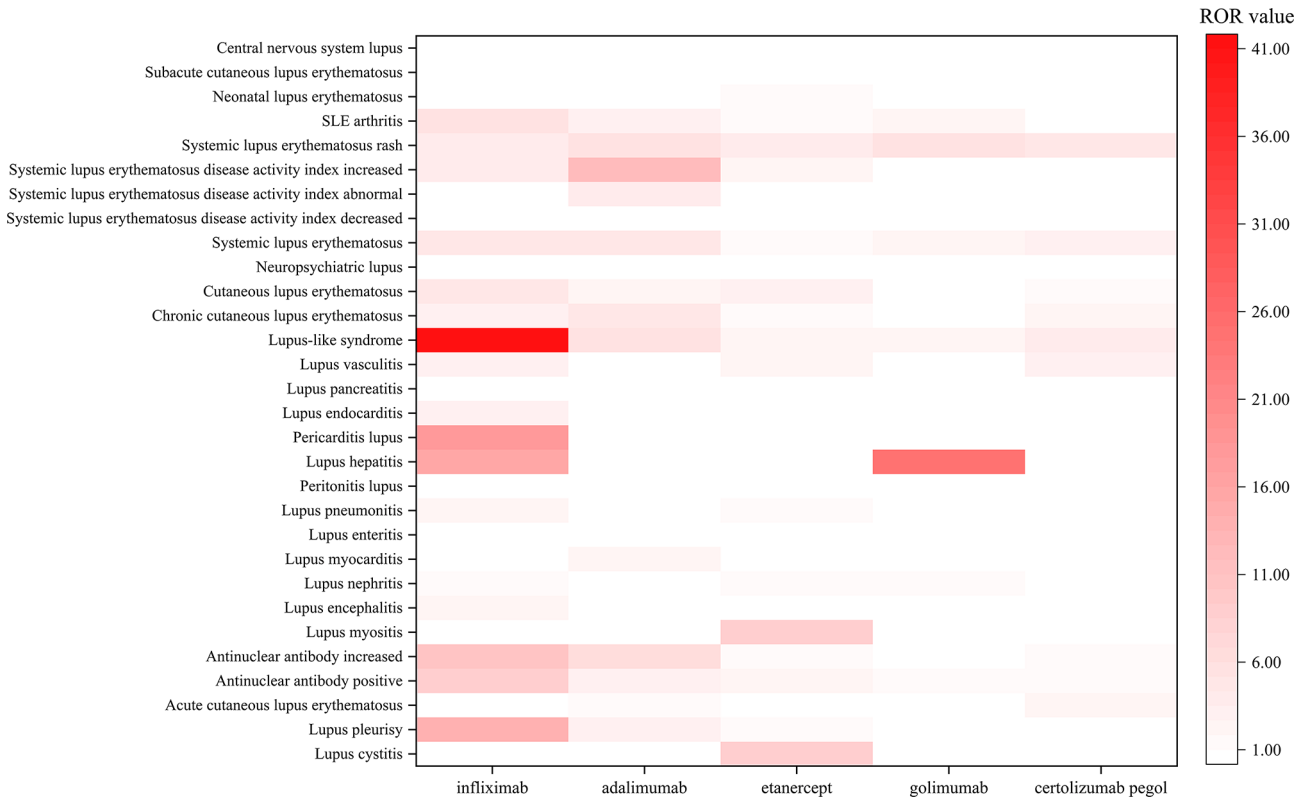
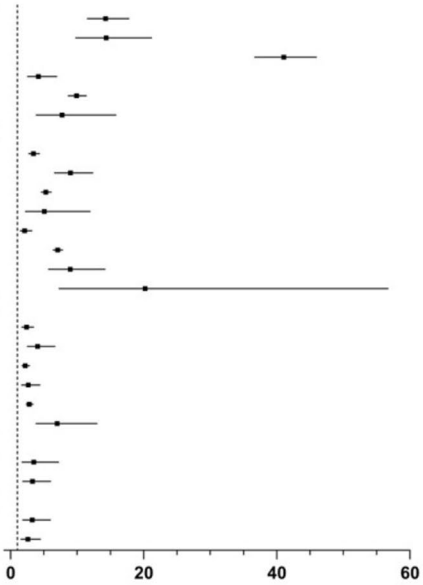


Fig. 3. PT-level heatmap of five TNF-α inhibitors-induced systemic lupus erythematosus.

Male

	a	ROR (95%CI)	IC (95%CI)
infliximab			
Antinuclear antibody positive	90	14.27 (11.43, 17.83)	3.64 (3.14, 3.79)
Antinuclear antibody increased	29	14.35 (9.7, 21.24)	3.64 (2.61, 3.73)
Lupus-like syndrome	428	41.05 (36.61, 46.02)	4.83 (4.58, 4.9)
Cutaneous lupus erythematosus	15	4.15 (2.47, 6.96)	2 (1.01, 2.49)
Systemic lupus erythematosus	205	9.89 (8.56, 11.42)	3.17 (2.9, 3.32)
Systemic lupus erythematosus rash	8	7.71 (3.74, 15.86)	2.84 (1.08, 3.08)
adalimumab			
Antinuclear antibody positive	66	3.4 (2.63, 4.38)	1.66 (1.24, 1.98)
Antinuclear antibody increased	48	8.98 (6.51, 12.39)	2.84 (2.2, 3.12)
Lupus-like syndrome	202	5.27 (4.54, 6.12)	2.21 (1.97, 2.4)
Chronic cutaneous lupus erythematosus	6	5.05 (2.13, 11.99)	2.16 (0.38, 2.74)
Cutaneous lupus erythematosus	22	2.1 (1.37, 3.24)	1.02 (0.33, 1.58)
Systemic lupus erythematosus	389	7.04 (6.31, 7.86)	2.56 (2.38, 2.7)
Systemic lupus erythematosus rash	23	8.94 (5.61, 14.23)	2.83 (1.84, 3.15)
SLE arthritis	6	20.21 (7.19, 56.77)	3.65 (0.9, 3.52)
etanercept			
Antinuclear antibody positive	26	2.36 (1.59, 3.49)	1.2 (0.57, 1.7)
Lupus nephritis	16	4.04 (2.43, 6.7)	1.94 (0.99, 2.44)
Lupus-like syndrome	50	2.17 (1.64, 2.88)	1.09 (0.64, 1.47)
Cutaneous lupus erythematosus	15	2.64 (1.57, 4.43)	1.36 (0.48, 1.96)
Systemic lupus erythematosus	96	2.78 (2.27, 3.41)	1.43 (1.11, 1.71)
Systemic lupus erythematosus rash	11	6.97 (3.73, 13.03)	2.66 (1.24, 3)
golimumab			
Lupus-like syndrome	7	3.45 (1.64, 7.25)	1.78 (0.37, 2.42)
Systemic lupus erythematosus	10	3.26 (1.75, 6.06)	1.7 (0.56, 2.3)
certolizumab pegol			
Lupus-like syndrome	10	3.24 (1.74, 6.03)	1.69 (0.55, 2.3)
Systemic lupus erythematosus	12	2.56 (1.45, 4.52)	1.35 (0.39, 1.99)



Female

	a	ROR (95%CI)	IC (95%CI)
infliximab			
Antinuclear antibody positive	188	9.57 (8.24, 11.12)	3.14 (2.86, 3.3)
Antinuclear antibody increased	62	11.55 (8.88, 15.03)	3.38 (2.8, 3.56)
Pericarditis lupus	4	29.63 (9.66, 90.87)	4.52 (0.62, 3.54)
Lupus-like syndrome	1646	52.17 (49.13, 55.39)	5.09 (4.98, 5.14)
Chronic cutaneous lupus erythematosus	7	4.21 (1.98, 8.98)	2.03 (0.51, 2.6)
Cutaneous lupus erythematosus	69	5.74 (4.51, 7.32)	2.45 (2.01, 2.72)
Systemic lupus erythematosus	1004	5.39 (5.06, 5.74)	2.36 (2.26, 2.45)
Systemic lupus erythematosus rash	23	4.54 (2.99, 6.9)	2.13 (1.34, 2.54)
SLE arthritis	14	9.7 (5.6, 16.8)	3.15 (1.76, 3.32)
adalimumab			
Antinuclear antibody positive	237	2.88 (2.51, 3.29)	1.41 (1.2, 1.6)
Antinuclear antibody increased	99	4.61 (3.72, 5.73)	2 (1.64, 2.27)
Lupus-like syndrome	831	4.81 (4.46, 5.18)	2.05 (1.93, 2.15)
Chronic cutaneous lupus erythematosus	31	5.1 (3.45, 7.53)	2.12 (1.41, 2.52)
Cutaneous lupus erythematosus	101	2.01 (1.64, 2.46)	0.95 (0.63, 1.23)
Systemic lupus erythematosus	2789	3.86 (3.7, 4.01)	1.78 (1.72, 1.84)
Systemic lupus erythematosus disease activity index increased	4	8.13 (2.59, 25.55)	2.64 (0.09, 3.05)
Systemic lupus erythematosus rash	98	5.31 (4.26, 6.62)	2.16 (1.79, 2.43)
SLE arthritis	16	2.61 (1.56, 4.38)	1.29 (0.43, 1.9)
etanercept			
Antinuclear antibody positive	122	1.77 (1.48, 2.13)	0.79 (0.51, 1.05)
Lupus-like syndrome	268	1.72 (1.52, 1.95)	0.75 (0.56, 0.93)
Cutaneous lupus erythematosus	87	2.18 (1.75, 2.71)	1.06 (0.73, 1.36)
Systemic lupus erythematosus	952	1.5 (1.41, 1.6)	0.56 (0.47, 0.66)
Systemic lupus erythematosus rash	48	2.95 (2.19, 3.97)	1.47 (0.98, 1.85)
golimumab			
Antinuclear antibody positive	90	14.27 (11.43, 17.83)	3.64 (3.14, 3.79)
Antinuclear antibody increased	29	14.35 (9.7, 21.24)	3.64 (2.61, 3.73)
Lupus-like syndrome	428	41.05 (36.61, 46.02)	4.83 (4.58, 4.9)
Cutaneous lupus erythematosus	15	4.15 (2.47, 6.96)	2 (1.01, 2.49)
Systemic lupus erythematosus	205	9.89 (8.56, 11.42)	3.17 (2.9, 3.32)
Systemic lupus erythematosus rash	8	7.71 (3.74, 15.86)	2.84 (1.08, 3.08)
certolizumab pegol			
Lupus-like syndrome	92	3.71 (3.02, 4.56)	1.87 (1.53, 2.13)
Systemic lupus erythematosus	280	2.78 (2.47, 3.13)	1.46 (1.28, 1.63)
Systemic lupus erythematosus rash	10	3.71 (1.98, 6.94)	1.87 (0.68, 2.44)

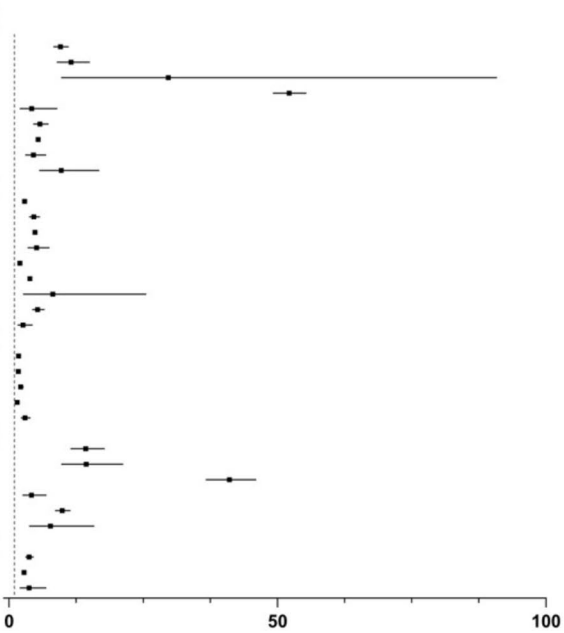


Fig. 4. Results of five TNF-α inhibitors-induced systemic lupus erythematosus at the PT level in gender subgroups.

highest degree of association with adalimumab; and lupus nephritis was not detected in the female group with etanercept.

Disproportionality analysis of age subgroups

In the age subgroup analysis, the positive signals detected by both methods were plotted in a forest plot according to their ROR values and 95% CI (Fig. 5a, b, c and d).

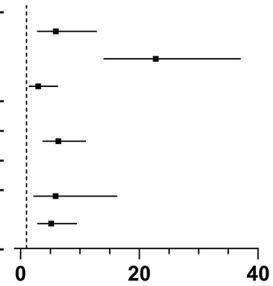
The association between etanercept and lupus nephritis in the Children age group ($n = 4$, ROR 5.89, 95% CI 2.14–16.27) was noteworthy.

In the Young Adults age group, signals of higher risk were adalimumab causing SLE arthritis ($n = 4$, ROR 25.32, 95% CI 6.33–101.24), and infliximab causing lupus-like syndrome ($n = 99$, ROR 14.34, 95% CI 11.36–18.09).

In the Adults age group, signals of higher risk were infliximab-induced lupus-like syndrome ($n = 1002$, ROR 37.56, 95% CI 34.79–40.54), and adalimumab-induced systemic lupus erythematosus disease activity index increased ($n = 4$, ROR 11.42, 95% CI 3.44–37.93).

(a)

infliximab	a	ROR (95%CI)	IC (95%CI)
Antinuclear antibody positive	7	5.94 (2.75, 12.83)	2.48 (0.76, 2.88)
Lupus-like syndrome	21	22.76 (13.96, 37.1)	4.14 (2.63, 4.01)
Systemic lupus erythematosus	7	2.95 (1.39, 6.29)	1.53 (0.17, 2.26)
adalimumab			
Systemic lupus erythematosus	14	6.36 (3.69, 10.98)	2.57 (1.38, 2.93)
etanercept			
Lupus nephritis	4	5.89 (2.14, 16.27)	2.48 (0.19, 2.87)
Systemic lupus erythematosus	11	5.15 (2.8, 9.48)	2.29 (1.02, 2.74)



(b)

infliximab	a	ROR (95%CI)	IC (95%CI)
Antinuclear antibody positive	12	3.1 (1.72, 5.59)	1.55 (0.51, 2.18)
Antinuclear antibody increased	6	8.74 (3.59, 21.31)	2.86 (0.71, 3.12)
Lupus-like syndrome	99	14.34 (11.36, 18.09)	3.4 (2.94, 3.59)
Systemic lupus erythematosus	38	2.13 (1.54, 2.96)	1.05 (0.53, 1.48)
adalimumab			
Antinuclear antibody positive	15	2.75 (1.62, 4.69)	1.37 (0.47, 1.98)
Lupus-like syndrome	44	3.63 (2.65, 4.98)	1.72 (1.19, 2.1)
Cutaneous lupus erythematosus	5	4.08 (1.59, 10.5)	1.87 (0.05, 2.59)
Systemic lupus erythematosus	70	2.87 (2.24, 3.68)	1.42 (1.03, 1.75)
SLE arthritis	4	25.32 (6.33, 101.24)	3.72 (0.29, 3.51)
etanercept			
Antinuclear antibody positive	7	2.98 (1.39, 6.36)	1.53 (0.17, 2.26)
Cutaneous lupus erythematosus	4	7.76 (2.75, 21.95)	2.81 (0.28, 3.03)
Systemic lupus erythematosus	29	2.74 (1.89, 3.97)	1.41 (0.8, 1.87)
certolizumab pegol			
Systemic lupus erythematosus	6	3.06 (1.37, 6.84)	1.6 (0.14, 2.33)

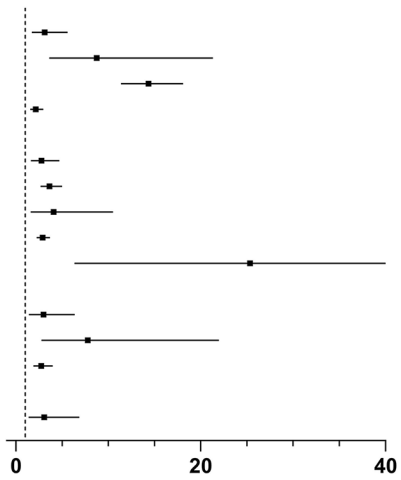


Fig. 5. (**a**) Results of five TNF-α inhibitors-induced systemic lupus erythematosus at the PT level in Children subgroup, (**b**) Results of five TNF-α inhibitors-induced systemic lupus erythematosus at the PT level in Young Adults subgroup, (**c**) Results of five TNF-α inhibitors-induced systemic lupus erythematosus at the PT level in Adults subgroup, (**d**) Results of five TNF-α inhibitors-induced systemic lupus erythematosus at the PT level in Elderly subgroup.

In the Elderly age group, certolizumab had the highest association with systemic lupus erythematosus rash ($n = 4$, ROR 15.34, 95% CI 5.67–41.49).

For the five TNF-α inhibitors, the positive signals with SLE were detected jointly in all four age groups. Infliximab had the highest number of positive signals detected in all four age groups and both PTs, lupus-like syndrome and systemic lupus erythematosus, were detected with more advanced signal intensity. Signals of interest included etanercept for lupus nephritis in the children group (ROR 5.89, 95% CI 2.14–16.27), and adalimumab for SLE arthritis in the young adults group (ROR 25.32, 95% CI 6.33–101.24) with high signal intensity.

Discussion

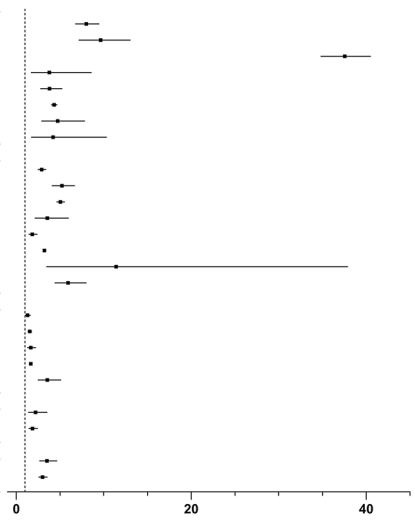
Infliximab (Remicade), adalimumab (Humira), etanercept (Enbrel), golimumab (Simponi Aria), and certolizumab pegol (Cimzia) are widely used as biologics for the treatment of autoimmune disorders in clinical practice. However, the treatment process may induce autoimmune diseases and the production of autoantibodies such as ANA and anti-dsDNA, causing a syndrome called drug-induced lupus (DIL), drug-induced lupus-like syndrome (DILS), or drug-induced lupus erythematosus (DILE), and more specifically TNF-α inhibitors-induced Systemic Lupus Erythematosus (TAILS), whose clinical features overlap with those of spontaneous SLE. Therefore, this study selected reports of TNF-α inhibitors-induced SLE according to the narrow set of SMQ terms in MedDRA, identifying more than 10,000 reports, making this study the largest and most extensive pharmacovigilance study on systemic lupus erythematosus associated with TNF-α inhibitors leveraging FAERS database.

Baseline characteristics of the five TNF-α inhibitors-induced SLE

In this study, 12,080 reports of TNF-α inhibitors as the primary suspected drug causing SLE were identified. In terms of the epidemiology of the cases, a clear female predominance was observed, with a higher proportion of female patients (64–86%), which is consistent with the findings of previous studies[24]. The median age distribution of the patients in this study was between 45 and 52 years, which corroborates the findings of the mean age of onset of 46.2 to 50.9 years mentioned in the studies by Wetter Da et al.[25] and Ramos-Casals M et al.[26].

(c)

infliximab	a	ROR (95%CI)	IC (95%CI)
Antinuclear antibody positive	147	8.01 (6.75, 9.49)	2.87 (2.56, 3.06)
Antinuclear antibody increased	48	9.65 (7.14, 13.05)	3.11 (2.46, 3.33)
Lupus-like syndrome	1002	37.56 (34.79, 40.54)	4.64 (4.5, 4.71)
Chronic cutaneous lupus erythematosus	6	3.79 (1.67, 8.61)	1.87 (0.27, 2.52)
Cutaneous lupus erythematosus	38	3.8 (2.74, 5.27)	1.87 (1.3, 2.25)
Systemic lupus erythematosus	568	4.32 (3.97, 4.7)	2.04 (1.91, 2.16)
Systemic lupus erythematosus rash	16	4.74 (2.86, 7.86)	2.17 (1.17, 2.62)
SLE arthritis	5	4.2 (1.7, 10.35)	2.01 (0.19, 2.63)
adalimumab			
Antinuclear antibody positive	164	2.9 (2.46, 3.41)	1.42 (1.17, 1.64)
Antinuclear antibody increased	75	5.22 (4.06, 6.71)	2.15 (1.72, 2.44)
Lupus-like syndrome	527	5.05 (4.59, 5.55)	2.11 (1.96, 2.24)
Chronic cutaneous lupus erythematosus	16	3.55 (2.1, 6.01)	1.68 (0.75, 2.24)
Cutaneous lupus erythematosus	56	1.84 (1.4, 2.42)	0.83 (0.41, 1.21)
Systemic lupus erythematosus	1229	3.21 (3.03, 3.41)	1.56 (1.47, 1.64)
Systemic lupus erythematosus disease activity index increased	4	11.42 (3.44, 37.93)	2.99 (0.18, 3.21)
Systemic lupus erythematosus rash	53	5.93 (4.39, 8.03)	2.3 (1.76, 2.62)
etanercept			
Antinuclear antibody positive	72	1.29 (1.02, 1.64)	0.36 (0, 0.7)
Lupus-like syndrome	169	1.54 (1.31, 1.79)	0.59 (0.36, 0.81)
Cutaneous lupus erythematosus	47	1.66 (1.24, 2.24)	0.7 (0.25, 1.11)
Systemic lupus erythematosus	619	1.65 (1.52, 1.79)	0.69 (0.57, 0.8)
Systemic lupus erythematosus rash	32	3.55 (2.45, 5.13)	1.69 (1.06, 2.12)
golimumab			
Lupus-like syndrome	17	2.2 (1.37, 3.55)	1.13 (0.36, 1.72)
Systemic lupus erythematosus	49	1.85 (1.4, 2.45)	0.89 (0.45, 1.27)
certolizumab pegol			
Lupus-like syndrome	47	3.51 (2.63, 4.68)	1.79 (1.3, 2.14)
Systemic lupus erythematosus	138	3.01 (2.54, 3.56)	1.57 (1.31, 1.8)



(d)

infliximab	a	ROR (95%CI)	IC (95%CI)
Antinuclear antibody positive	17	6.56 (4.04,10.65)	2.67 (1.6,2.98)
Antinuclear antibody increased	6	11.55 (5.05,26.41)	3.44 (1.04,3.3)
Lupus-like syndrome	86	21.99 (17.57,27.53)	4.29 (3.68,4.34)
Cutaneous lupus erythematosus	15	5.76 (3.45,9.64)	2.49 (1.39,2.85)
Systemic lupus erythematosus	55	6.81 (5.2,8.92)	2.72 (2.19,2.97)
adalimumab			
Antinuclear antibody positive	27	2.82 (1.91,4.16)	1.44 (0.79,1.91)
Antinuclear antibody increased	10	5.33 (2.77,10.27)	2.29 (0.92,2.76)
Lupus-like syndrome	69	4.55 (3.55,5.82)	2.08 (1.65,2.37)
Systemic lupus erythematosus	130	4.5 (3.76,5.39)	2.07 (1.77,2.29)
Systemic lupus erythematosus rash	13	4.79 (2.71,8.49)	2.15 (1.01,2.63)
etanercept			
Antinuclear antibody increased	7	3.75 (1.74,8.1)	1.83 (0.36,2.48)
Lupus-like syndrome	39	2.56 (1.86,3.54)	1.31 (0.79,1.73)
Systemic lupus erythematosus	88	3.07 (2.48,3.81)	1.56 (1.21,1.84)
Systemic lupus erythematosus rash	7	2.56 (1.2,5.48)	1.31 (0.01,2.11)
certolizumab pegol			
Lupus-like syndrome	5	3.37 (1.4,8.11)	1.74 (0.08,2.45)
Systemic lupus erythematosus	14	4.98 (2.94,8.43)	2.3 (1.22,2.72)
Systemic lupus erythematosus rash	4	15.34 (5.67,41.49)	3.9 (0.66,3.29)

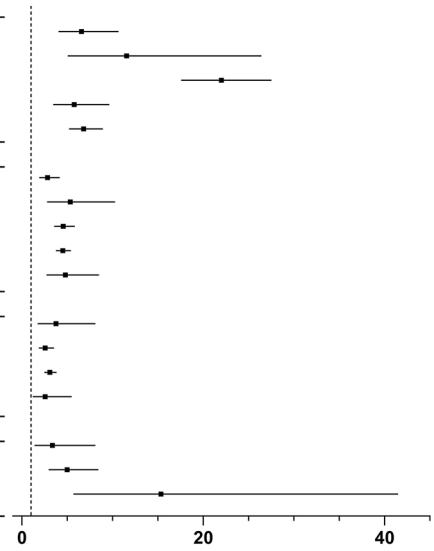


Figure 5. (continued)

The median onset time from the initiation of treatment with TNF-α inhibitors to the development of SLE ranged from about 1 month to 10 months. Infliximab, adalimumab, and etanercept had longer median onset times (over 7 months), while golimumab and certolizumab pegol had median onset times around one or two months. R. Perez- Alvarez et al. showed that the time to onset of SLE symptoms after initiation of TNF-α inhibitors ranged from 10 days to 54 months[5,27]. The median time to onset of SLE varied among the different TNF-α inhibitors, with the highest number of reports of SLE induced within 90 days of administration. The half-life of TNF-α inhibitors varies[28] (infliximab: 8–9.5 d, adalimumab with certolizumab: 14 d, etanercept: 70 h, golimumab: 13 d), the above findings suggest that SLE may still occur even after patients have stopped treatment with the drugs, and that the risk of drug-induced SLE needs to be continuously monitored for a long period of time.

Of the 12,080 reports collected in this study, 93.37% were serious reports, which may lead to serious outcomes such as hospitalization-initial or prolonged and other serious medical events, and even fatal outcomes. Certolizumab pegol and etanercept were associated with the highest proportion of fatal outcomes, suggesting a higher likelihood of fatal consequences with these drugs. Therefore, vigilance and timely preventive measures are necessary if SLE occurs during treatment. This also highlights the importance of considering the risk of death associated with lupus-related clinical diagnosis and treatment activities, while also taking into account other factors contributing to mortality, such as disease progression. Several risk factors have been identified for TNF-α inhibitors-induced systemic lupus erythematosus[29], including female gender, older age, family history of systemic lupus erythematosus, and elevated levels of anti-dsDNA antibodies prior to anti-TNF-α treatment, emphasizing the importance of early identification and proactive prevention during the use of TNF-α inhibitors in clinical practice.

Risk of the five TNF-α inhibitors-induced SLE

TNF-α inhibitors, as immunotherapy, may interfere with specific immune pathways during treatment, potentially activating compensatory signaling pathways that exacerbate underlying subclinical diseases or lead to autoimmune conditions completely different from the underlying disease[2,29]. TNF-α inhibitors-induced systemic lupus erythematosus poses a major challenge during the treatment process.

In this study, focusing on the SMQ narrow term of SLE, infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol all showed significant signals in the overall population, with infliximab presenting the highest risk followed by adalimumab. Laurent Arnaud et al.[10] utilized the VigiBase database to identify 8,163 reports with PT as systemic lupus erythematosus, involving 118 suspected drugs, with TNF-α inhibitors being the most common suspected drugs ($n = 2,793$), and the drugs with the highest number of case reports were infliximab ($n = 1,055$, IC025 3.39) and adalimumab ($n = 926$, IC025 1.66), which is consistent with the results of this study, thereby validating the reliability of the findings to a certain extent.

Differences in the structure and pharmacokinetics of different TNF-α inhibitors may result in varying risks of inducing SLE for each drug[30]. In other words, although the mechanism of action of TNF-α inhibitors is similar, due to the different in vivo pharmacokinetics of each drug, the structural differences bring about different receptor membrane binding strengths, different phagocytosis and clearing ability of ANA, and the degree of impact on safety is also different, which can also explain the results of the present study in which the risk of SLE induced by different TNF-α inhibitors varies. In the case of infliximab, its chimeric structure makes it considered the most immunogenic of the TNF-α inhibitors, allowing it to reach higher tissue concentrations, which may increase cytotoxicity and stimulate autoantibody production, thereby increasing the risk of TAILS.

Reports indicated[31] that the TNF-α inhibitors with the highest rates of inducing lupus were INF, followed by ADA, then ETN, while GM and CZP had few reports of inducing TAILS. In the large population male subgroup of this study, the risk of TNF-α inhibitors inducing SLE from highest to lowest is infliximab > adalimumab > etanercept > golimumab > certolizumab pegol; in the four age subgroups, infliximab poses the highest risk of inducing SLE, followed by adalimumab and etanercept, consistent with the aforementioned study results.

Of note, in the overall population, etanercept carries the lowest risk of inducing SLE; in the female patient subgroup, golimumab poses the highest risk, while etanercept has the lowest risk. This discrepancy from previous reports is likely due to factors such as the production of autoantibodies related to gender, age, underlying diseases, medication history, infection status, and other factors. Additionally, in the real world, the complexity of different host immune systems' sensitivity to various drugs can impact the production of autoantibodies to varying degrees, leading to differing risks of each TNF-α inhibitor inducing systemic lupus erythematosus in different patient subgroups[32]. Compared to existing research, the results of this study based on a vast amount of FAERS records will provide valuable clinical evidence, highlighting the need for future research to focus on and monitor the differences in the risk of TNF-α inhibitors inducing TAILS in various patient subgroups.

Distinct signals of the five TNF-α inhibitors-induced SLE

TNF-α inhibitors-induced autoimmune lesions of systemic lupus erythematosus (TAILS) can be categorized as anti-TNF-α induced lupus (ATIL), lupus-like syndrome, and isolated autoimmune lesions. In most cases, TAILS is characterized by skin manifestations, high titers of ANA and anti-dsDNA, and generally by arthralgia and arthritis, with rare involvement of organs such as the kidneys and heart.

In this study, five TNF-α inhibitors were significantly associated with lupus-like syndrome, systemic lupus erythematosus and systemic lupus erythematosus rash, and the association of antinuclear antibody positive, and antinuclear antibody increased was also more significant, which is in line with Ramos-Casals et al. They found that the clinical manifestations of 72 cases of TAILS were predominantly positive ANA (57 cases, 79%), positive anti-dsDNA (52 cases, 72%), and skin symptoms (48 cases, 66.67%).

The results of this study indicate that adalimumab poses a higher risk of SLE arthritis in the male subgroup (ROR 20.21, 95% CI 7.19–56.77), while in the female subgroup, the signal strength for SLE arthritis is 2.61 (1.56, 4.38), and for infliximab, it is 9.7 (95% CI 5.6–16.8). Arthritis is the first feature observed in a single-center patient cohort in previous studies (71% of cases), and usually occurs more frequently in women than in men[25]. The results of this study suggest a similarly high risk of joint involvement in male patients, which warrants clinical attention, especially during treatment with adalimumab. Arthritis is usually the initial symptom of systemic lupus erythematosus in patients, often accompanied by significant inflammation, with a potential for erosive arthritis (EA) leading to irreversible functional damage. When patients experience joint pain or discomfort during treatment, relevant investigations should be conducted for early diagnosis and management.

Serum ANA and anti-dsDNA titers are elevated in patients treated with TNF-α inhibitors, and vasculitis caused by high levels of pathogenic autoantibodies and immune complex deposition in the serum can further lead to impaired multiorgan function in patients. Two patient series conducted in the United States and Spain reported renal involvement in 7% and 9% of TAILS patients[5]. In addition, one study[33]investigated 29 cases of biologic-induced autoimmune renal disorders (AIRD), in which etanercept (15 cases, 51.7%) was the most relevant drug, including four cases of glomerulonephritis in lupus-like syndrome (GNP). The mean age of onset in cases of lupus-like syndrome (GNLS) was 37.0 years (ranging from 22 to 52 years). There have been numerous case reports of lupus nephritis caused by etanercept[34–38], including life-threatening cases resulting in death[9].

Importantly, the present study observed some degree of risk association between etanercept and lupus nephritis in the children subgroup compared to other age groups (ROR 5.89, 95% CI 2.14–16.27). The risk of lupus nephritis observed in the children age group (0–14 years) in this study may be due to the fact that children are more susceptible to organ involvement because of incomplete organ development, in addition to the fact that etanercept as a biologic agent promotes the development of glomerulonephritis in lupus-like syndrome. Lupus nephritis, as a complication that seriously affects the prognosis, has a severe clinical manifestation and poor

prognosis, and is one of the major causes of death. In the course of clinical treatment with TNF-α inhibitors such as etanercept, children should be alerted to the possibility of lupus nephritis, and should be screened regularly with renal parameters such as urinalysis, proteinuria quantification, and estimation of glomerular filtration rate, so as to achieve continuous management of children, in order to avoid the development of lupus nephritis and the further induction of acute kidney injury and other adverse effects.

Other rare and severe clinical features include pleurisy with pericarditis, pericardial effusion or pleural effusion. The results of this study observed an association between infliximab-induced lupus pericarditis in a subgroup of female patients (ROR 29.63, 95% CI 9.66–90.87) and the overall population (ROR 17.98, 95% CI 6.75–47.90), and a risk of lupus pleurisy induction in the overall population (ROR 13.83, 95% CI 5.31–36.01) risk. Complications such as pericarditis, pleurisy and pleural effusion induced by infliximab are less well documented. In recent years, a case of TAILS, manifested by pleural effusion and pericarditis, was reported in an 18-year-old patient treated with infliximab[39]. A study also reported a case of large pericardial effusion secondary to ATILS in a patient taking infliximab for long-term treatment of ulcerative colitis large pericardial effusion, which led to initial cardiac tamponade[40].

Mechanisms regarding clinical features such as infliximab-induced pericarditis lupus are unclear and may be related to direct cardiotoxicity, immunoglobulin E-mediated anaphylactic reactions, humoral antibody responses, cell-mediated delayed hypersensitivity, and serum sickness-like reactions[41]. Healthcare professionals need to be vigilant for further cardiac and thoracic involvement by infliximab-induced TAILS, closely monitor patients' cardiac function, and intervene promptly in the event of dyspnea, hypotension, dizziness, and cephalic colic in an effort to minimize the risk of life-threatening events.

Therapeutic management of the five TNF-α inhibitors-induced SLE

The symptoms associated with TAILS range from common mild skin symptoms to complications such as arthritis, nephritis, and rare and life-threatening conditions like pericardial effusion and pleuritis. Early identification and strict follow-up of any complications that arise in patients receiving TNF-α inhibitors are crucial to ensuring the long-term safety of the patients.

The Spanish Autoimmune Disease Biologics Study Group (BIOGEAS) has developed management guidelines for autoimmune diseases related to TNF-α inhibitors, emphasizing the customization of treatment plans based on the severity of individual disease manifestations[5]. If TAILS is limited to skin or serological features, it can be controlled by simply discontinuing the medication. However, if organ involvement such as renal or cardiac impairment is present, mandatory cessation of the medication is required, along with the addition of corticosteroids and immunosuppressants to prevent further complications. The British Society for Rheumatology also explicitly advises discontinuing pathogenic anti-tumor necrosis factor drugs in TAILS patients.

Furthermore, healthcare professionals need to exercise caution when using TNF-α inhibitors and conduct comprehensive immunological screening when considering the use of these biologics. This screening should include baseline immunological analysis and chest X-ray examinations before treatment, with specific time-bound follow up centered on the possible development of cutaneous, articular, or renal manifestations.

Conclusions and limitations

This study conducted a retrospective analysis based on the FAERS database, systematically investigating the association between different TNF-α inhibitors and SLE. We raised concerns regarding the potential risk of systemic lupus erythematosus associated with TNF-α inhibitors, as indicated in the SMQ cluster analysis. The specific PT signals involved adalimumab inducing SLE arthritis in the male subgroup, etanercept causing lupus nephritis in the children subgroup, and infliximab leading to pericarditis lupus and lupus pleurisy. The results suggest that the systemic manifestations of TNF-α inhibitors-induced SLE range from mild to rare and life-threatening symptoms, including skin involvement, arthritis, pleuritis, pericarditis, and renal impairment. This information highlights the need for clinicians to be vigilant about the potential risks in patients receiving TNF-α inhibitors, continuously monitor for lupus toxicity during treatment, and may provide a novel basis for further well-organized clinical investigations into SLE related to TNF-α inhibitors.

This study has several advantages, particularly in the areas of real-world research and data mining techniques; however, it also has some limitations. Firstly, the FAERS is a spontaneous reporting system, which may result in variability in information sources, potential data duplication, and data irregularities, making it difficult to control the quantity and quality of reports. Secondly, although we collected a large amount of basic demographic data from patients, their overall health status and complete medication history were not sufficiently clear, introducing potential confounding factors and uncertainties into our analysis. Lastly, the research methodology cannot eliminate the influence of factors such as underlying diseases and concomitant medications. Therefore, the analytical results only support a statistical correlation, and whether a causal relationship exists should be considered in conjunction with evidence from evidence-based medicine.

Data availability

Publicly available datasets were analyzed in this study. This data can befound here: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

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References

1. Ghorbaninezhad, F. et al. Tumor necrosis factor–α in systemic lupus erythematosus: structure, function and therapeutic implications (review). *Int. J. Mol. Med.* **49**, 43. https://doi.org/10.3892/ijmm.2022.5098 (2022).
2. Kremenevski, I., Sander, O., Sticherling, M., Raithel, M. & LastName, F. M. Paradoxical reactions to biologicals in chronic inflammatory systemic diseases. *Dtsch. Arzteblatt Int.* **119**, 88–95. https://doi.org/10.3238/arztebl.m2022.0067 (2022).
3. Aggarwal, B. B., Gupta, S. C. & Kim, J. H. Historical perspectives on tumor necrosis factor and its superfamily: 25 years later, a golden journey. *Blood* **119**, 651–665. https://doi.org/10.1182/blood-2011-04-325225 (2012).
4. Shivaji, U. N. et al. Review article: managing the adverse events caused by anti-TNF therapy in inflammatory bowel disease. *Aliment. Pharmacol. Ther.* **49**, 664–680. https://doi.org/10.1111/apt.15097 (2019).
5. Pérez-De-Lis, M. et al. Autoimmune diseases induced by biological agents. A review of 12,731 cases (BIOGEAS Registry). *Expert Opin. Drug Saf.* **16**, 1255–1271. https://doi.org/10.1080/14740338.2017.1372421 (2017).
6. Eriksson, C., Engstrand, S., Sundqvist, K-G. & Rantapää-Dahlqvist, S. Autoantibody formation in patients with rheumatoid arthritis treated with anti-TNF alpha. *Ann. Rheum. Dis.* **64**, 403–407. https://doi.org/10.1136/ard.2004.024182 (2005).
7. Aghdashi, M. A., Khadir, M. & Dinparasti-Saleh, R. Antinuclear Antibodies and lupus-like manifestations in Rheumatoid Arthritis and Ankylosing Spondylitis patients at 4 months' follow-up after treatment with Infliximab and Etanercept. *Curr. Rheumatol. Rev.* **16**, 61–66. https://doi.org/10.2174/1573397115666190506152729 (2020).
8. Atzeni, F. & Sarzi-Puttini, P. Autoantibody production in patients treated with anti-TNF-alpha. *Expert Rev. Clin. Immunol.* **4**, 275–280. https://doi.org/10.1586/1744666X.4.2.275 (2008).
9. Sacquépée, M. et al. Tivollier J-M. active WHO class IV lupus nephritis in a patient treated with etanercept for a psoriasic arthritis. *Nephrol. Ther.* **6**, 537–540. https://doi.org/10.1016/j.nephro.2010.05.003 (2010).
10. Arnaud, L. et al. Drug-induced systemic lupus: revisiting the ever-changing spectrum of the disease using the WHO pharmacovigilance database. *Ann. Rheum. Dis.* **78**, 504–508. https://doi.org/10.1136/annrheumdis-2018-214598 (2019).
11. CIOMS Working Group. *Practical Aspects of Signal Detection in Pharmacovigilance* (Council for International Organizations of Medical Sciences, 2010).
12. Peng, L., Xiao, K., Ottaviani, S., Stebbing, J. & Wang, Y-J. A real-world disproportionality analysis of FDA adverse event reporting System (FAERS) events for baricitinib. *Expert Opin. Drug Saf.* **19**, 1505–1511. https://doi.org/10.1080/14740338.2020.1799975 (2020).
13. Tregunno, P. M., Fink, D. B., Fernandez-Fernandez, C., Lázaro-Bengoa, E. & Norén, G. N. Performance of probabilistic method to detect duplicate individual case safety reports. *Drug Saf.* **37**, 249–258. https://doi.org/10.1007/s40264-014-0146-y (2014).
14. Zhou, Y. et al. Anti-tumor necrosis factor-alpha therapy and hypoglycemia: a real-world pharmacovigilance analysis. *Drug Saf.* **45**, 951–959. https://doi.org/10.1007/s40264-022-01210-2 (2022).
15. Chen, H., Yang, G. & Ma, J. Ocular toxicity associated with anti-HER2 agents in breast cancer: a pharmacovigilance analysis using the FAERS database. *Int. J. Cancer*. **154**, 1616–1625. https://doi.org/10.1002/ijc.34848 (2024).
16. Almenoff, J. S. et al. Novel statistical tools for monitoring the safety of marketed drugs. *Clin. Pharmacol. Ther.* **82**, 157–166. https://doi.org/10.1038/sj.clpt.6100258 (2007).
17. Sakaeda, T., Tamon, A., Kadoyama, K. & Okuno, Y. Data mining of the public version of the FDA adverse event reporting system. *Int. J. Med. Sci.* **10**, 796–803. https://doi.org/10.7150/ijms.6048 (2013).
18. Ps, A., Z, C., Cl, C. & Bc, T. Data mining spontaneous adverse drug event reports for safety signals in Singapore - a comparison of three different disproportionality measures. *Expert Opin. Drug Saf.* **15**, https://doi.org/10.1517/14740338.2016.1167184 (2016).
19. Hou, Y. et al. A comparison of disproportionality analysis methods in national adverse drug reaction databases of China. *Expert Opin. Drug Saf.* **13**, 853–857. https://doi.org/10.1517/14740338.2014.915938 (2014).
20. Chen, Y. et al. Comparison of sensitivity and Timing of Early Signal Detection of Four Frequently Used Signal Detection Methods: an empirical study based on the US FDA adverse event reporting System Database. *Pharm. Med.* **22**, 359–365. https://doi.org/10.1007/BF03256733 (2008).
21. Chen, C., Zhou, R., Fu, F. & Xiao, J. Postmarket safety profile of suicide/self-injury for GLP-1 receptor agonist: a real-world pharmacovigilance analysis. *Eur. Psychiatry J. Assoc. Eur. Psychiatr.* **66**, e99. https://doi.org/10.1192/j.eurpsy.2023.2474 (2023).
22. 21 CFR 314.80. -- Postmarketing reporting of adverse drug experiences. https://www.ecfr.gov/current/title-21/part-314/section-314.80 [Accessed May 4, 2024].
23. Zhai, Y. et al. Endocrine toxicity of immune checkpoint inhibitors: a real-world study leveraging US Food and Drug Administration adverse events reporting system. *J. Immunother Cancer*. **7**, 286. https://doi.org/10.1186/s40425-019-0754-2 (2019).
24. De Bandt, M. et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. *Arthritis Res. Ther.* **7**, R545–551. https://doi.org/10.1186/ar1715 (2005).
25. Wetter, D. A. & Davis, M. D. P. Lupus-like syndrome attributable to anti-tumor necrosis factor alpha therapy in 14 patients during an 8-year period at Mayo Clinic. *Mayo Clin Proc.* **84** 979–984. (2009). https://doi.org/10.4065/84.11.979
26. Ramos-Casals, M. et al. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. *Med. (Baltim).* **86**, 242–251. https://doi.org/10.1097/MD.0b013e3181441a68 (2007).
27. R P-A, M P-L, M. R. C. Biologics-induced autoimmune diseases. *Curr. Opin. Rheumatol.* **25**, https://doi.org/10.1097/BOR.0b013e32835b1366 (2013).
28. Mengdi, S., Han, X., Xudong, M., Zhang, H. & Li, L. Perioperative Management of Tumor Necrosis Factor Alpha Inhibitors. *Herald Med.* 1–25 (2024).
29. De Stefano, L. et al. Tumor necrosis factor-α inhibitor-related autoimmune disorders. *Autoimmun. Rev.* **22**, 103332. https://doi.org/10.1016/j.autrev.2023.103332 (2023).
30. Xuecai, X., Lu, C., Xingxian, L. & Feng, W. Status of research on drug induced antibodies followingtreatment withtumor necrosis factor-a inhibitors. *Chin. J. Clin. Pharmacol.* **33**, 2089–2092. https://doi.org/10.13699/j.cnki.1001-6821.2017.20.026 (2017).
31. Jani, M. et al. Drug-specific risk and characteristics of lupus and vasculitis-like events in patients with rheumatoid arthritis treated with TNFi: results from BSRBR-RA. *RMD Open.* **3**, e000314. https://doi.org/10.1136/rmdopen-2016-000314 (2017).
32. Benucci, M., Saviola, G., Baiardi, P., Cammelli, E. & Manfredi, M. Anti-nucleosome antibodies as prediction factor of development of autoantibodies during therapy with three different TNFalpha blocking agents in rheumatoid arthritis. *Clin. Rheumatol.* **27**, 91–95. https://doi.org/10.1007/s10067-007-0728-5 (2008).
33. Piga, M. et al. Biologics-induced autoimmune renal disorders in chronic inflammatory rheumatic diseases: systematic literature review and analysis of a monocentric cohort. *Autoimmun. Rev.* **13**, 873–879. https://doi.org/10.1016/j.autrev.2014.05.005 (2014).
34. Haake, H., Köneke, J., Amann, K., vom Dahl, J. & Janssen, U. Development of systemic lupus erythematosus with focal proliferative lupus nephritis during anti-TNF-alpha therapy for psoriatic arthritis. *Med. Klin. Munich Ger. 1983.* **102**, 852–857. https://doi.org/10.1007/s00063-007-1104-6 (2007).
35. Mor, A., Bingham, C. O., Barisoni, L., Lydon, E. & Belmont, H. M. Proliferative lupus nephritis and leukocytoclastic vasculitis during treatment with etanercept. *J. Rheumatol.* **32**, 740–743 (2005).
36. Neradová, A., Stam, F., van den Berg, J. G. & Bax, W. A. Etanercept-associated SLE with lupus nephritis. *Lupus* **18**, 667–668. https://doi.org/10.1177/0961203308100560 (2009).
37. Stokes, M. B. et al. Development of glomerulonephritis during anti-TNF-alpha therapy for rheumatoid arthritis. *Nephrol. Dial Transpl. Off Publ Eur. Dial Transpl. Assoc. - Eur. Ren. Assoc.* **20**, 1400–1406. https://doi.org/10.1093/ndt/gfh832 (2005).
38. Yahya, T. M., Dhanyamraju, S., Harrington, T. M. & Prichard, J. W. Spontaneous resolution of lupus nephritis following withdrawal of etanercept. *Ann. Clin. Lab. Sci.* **43**, 447–449 (2013).

39. Fonseca, A., Sunny, J. & Felipez, L. M. Antitumor Necrosis factor-alpha (TNF-α) Infliximab-Induced Pleural Effusion and Pericarditis in Crohn's Disease. *Case Rep. Pediatr.* **2021**, 9989729. https://doi.org/10.1155/2021/9989729 (2021).
40. Harnett, D. T., Chandra-Sekhar, H. B. & Hamilton, S. F. Drug-Induced Lupus Erythematosus Presenting With Cardiac Tamponade: A Case Report and Literature Review. *Can. J. Cardiol.* (2014).
41. Dipasquale, V., Gramaglia, S. M. C., Catena, M. A. & Romano, C. Pericarditis during infliximab therapy in paediatric ulcerative colitis. *J. Clin. Pharm. Ther.* **43**, 107–109. https://doi.org/10.1111/jcpt.12586 (2018).

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Conception and design: MJ H. and PC L. Data analysis: MJ H. and JL Y. Interpretation of the data and draftin the paper: MJ H. and JL Y. and PC L. Critical revision of the paper for intellectual content: SM Y. QS. and PC L. Writing review and editing work: MJ H. and PC L. The final manuscript was read, checked and approved by all authors.

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Declarations

Competing interests
The authors declare no competing interests.

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