Clinical Features And Risk Factors For Infection In Patients With Rheumatoid Arthritis

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Research

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Abstract

Background: To explore the infection characteristics of patients with rheumatoid arthritis(RA) and related risk factors for infection.

Methods: A retrospective analysis of the clinical data of 648 hospitalized patients with RA, including related risk factors that may cause infection and infection sites, pathogens, and drug resistance. Chi-square test □Mann-Whitney U test and binary Logistic-regression analysis were used to identify risk factors.

Results: 648 patients with RA were 182 cases of infection, the infection rate 28.09%. Common infection were pneumonia(19.60%), urinary tract infection(5.25%), upper respiratory tract infection(5.09%). Gram-negative bacteria ranked first in the pathogen composition (67.57%), the main pathogenic bacteria were *Pseudomonas aeruginosa* and *Escherichia coli*; *Staphylococcus aureus* was the main pathogenic bacteria among the Gram-positive bacteria . In addition, there were 7 strains of fungi, 3 strains each of *Mycobacterium tuberculosis* and herpes virus. The proportion of resistant strains was relatively high, and the gram-negative bacteria had a relatively high sensitivity to penicillins/cephalosporins+β-lactamase inhibitors, aminoglycosides, and carbopenems. The risk scores included higher age ($P=0.020$), long diseases duration ($P=0.004$), smoking ($P=0.016$), hypoproteinemia ($P=0.010$), use of corticosteroids ($P<0.01$).Use of nonbiologic DMARDs was negatively with infection($P= 0.006$).

Conclusions: Our results indicate that the common infection sites in patients with RA are the respiratory and urinary tract. Gram-negative bacteria are common pathogens. RA patients with higher age, long diseases duration, smoking, hypoproteinemia, and long-term use of corticosteroids are prone to infection. Nonbiologic DMARDs is significantly associated with a decreased risk for infection. The proportion of drug-resistant patients with RA co-infection is relatively high.

Background

Rheumatoid arthritis(RA) is a chronic systemic autoimmune disease characterized by erosive and symmetrical polyarthritis that may lead to irreversible joint damage with disability and deformity .Patients with RA have increased susceptibility for infction,infection rate are reported to be almost twice those of the general population[1]. Numerous studies have reported endogenous and exogenous risk factors for infection in RA patients,attributed to three major factors:RA itself as a chronic disorder with immunological dysfuctions,organ involvement of RA and other comorbidities,as well as the use of potent immunomodulatory medication[2].This article retrospectively analyzed the clinical characteristics of infection in patients with RA in the past two years, aims to improve the understanding of RA complicated by infection, and reducec and prevent the occurrence of the infections.

Material And Methods

Patients Selection

From April 2017 to April 2019, inpatients with RA in the General Hospital of Northern Theater Command and the Fourth Affiliated Hospital of China Medical University (Patients with severe cerebrovascular diseases, malignant tumors, and individual clinical data missing severely were not included in the study). Patients fulfilled the 2010 American College of Rheumatology /European League Against Rheumatism criteria for RA[3]. The diagnosis of patients with RA co-infection had clear pathogenic biological□laboratory or imaging evidence, typical clinical manifestations. Some patients with infections that could be diagnosed by clinical manifestations, such as typical upper respiratory tract infections and patients with skin shingles diagnosed by a dermatologist, had not undergone relevant imaging or

laboratory examinations. The patients with RA co-infection collected in this study included community acquired infections and nosocomial infections[4].

Methods

We collected relevant data through the hospital's electronic medical record system, including general characteristics: age, gender, smoking, diseases duration; auxiliary examination: hemoglobin(HB), platelets(PLT), white blood cells(WBC), C-reactive protein(CRP), erythrocyte sedimentation rate(ESR), immunoglobulin A(IgA), immunoglobulin G(IgG), immunoglobulin M(IgM), rheumatoid factor(RF), anti-cyclic citrulline peptide antibody(anti-CCP), complement3(C3), complement4(C4) ; comorbidities; therapeutic drugs: corticosteroids, nonbiologic disease-modifying antirheumatic drugs(DMARDs), biological agents. Infection situation: infection site, pathogen culture and drug susceptibility results.

Statistical Analysis

Descriptive statistics were presented as mean $\pm$ SD or number (%) where appropriate. Non-normally distributed data were analyzed using nonparametric tests(Mann-Whitney U test). Chi-square test to test the association of categorical variables. Risk factors for infections were analyzed by multivariate analysis with binary logistic regression model. Continuous variables were transformed into categorical variables with a predetermined threshold. The p values less than 0.05 were considered significant. Statistical analysis was performed using SPSS software version 23 .

Results

Baseline Characteristics of the RA Patients

The study population comprised 648 patients with RA (505 women (78%), mean age 60 $\pm$ 12 years, mean diseases duration 10 $\pm$ 9 years).

Infection Rate of the RA Patients

A total of 648 patients with RA were 182 cases of infection, the infection rate 28.09%. Among them, 99 cases of 517 RA patients in the Department of Rheumatology and Immunology were infected, and the infection rate was 19.15%. The incidence of infection in the whole hospital was higher than that of the Department of Rheumatology and Immunology. 21 cases were infected at 2 sites at the same time, 2 cases were infected at 3 sites. Community-acquired infections were 175 cases, 7 cases of hospital-acquired infections.

Infection Site of the RA Patients

The pneumonia was the most frequent infection ($n = 127$, 19.60%) followed by the urinary tract ($n = 34$, 5.25%), upper respiratory tract ($n = 33$, 5.09%). 3 cases each of herpes virus and tuberculosis, 2 cases of skin and soft tissue infection, 1 case each of oral fungus, knee joint, and muscle infection.

Infection Pathogens of the RA Patients

A total of 74 strain pathogens were isolated and cultured from 182 infected patients. Bacteria was the most common pathogen, with 50 strains in total, among which 40 were gram-negative bacteria. Escherichia coli and Pseudomonas aeruginosa were the most common and caused urinary tract and respiratory tract infections respectively. There were 10 strains of Gram-positive bacteria, 9 of which were Staphylococcus aureus, which mainly cause respiratory tract infections, and 1 strain was Enterococcus hirae, which caused urinary tract infections. There were 11 strains of

Mycoplasma and Chlamydia, two of which were Ureaplasma Urealyticum caused urinary tract infections, and the rest caused respiratory infections. There were 7 strains of fungi, 5 strains of Candida albicans caused respiratory and oral infections, and 2 strains of yeast-like fungi caused urinary tract infections. Three strains of Mycobacterium tuberculosis and herpes virus respectively caused tuberculosis and skin herpes(Table 1).

Table 1 The composition of pathogens in RA with infection

Pathogen	Respiratory tract	Urinary tract	Skin and soft issue	Oral cavity	Bone and joint
Gram-negative bacteria					
Pseudomonas aeruginosa	9	1			
Escherichia coli		11			
Unclassified Enterobacter	6				
Haemophilus influenzae	3				
Stenotrophomonas	3				
maltophilia	3				
Klebsiella pneumoniae	1				
Acinetobacter baumannii	2	1			
Other					
Gram-positive bacteria	8				1
Staphylococcus aureus		1			
Enterococcus hirae					
Fungus	4			1	
Candida albicans		2			
Yeast-Like fungi					
Virus			3		
Herpesvirus	3				
Mycobacterium tuberculosis					
Mycoplasma/ Chlamydia	2				
Chlamydia		2			
Ureaplasma Urealyticum	7				
Other mycoplasma					

Antimicrobial Susceptibility Results

In this study, 27 strains of gram-negative bacteria were isolated for drug susceptibility testing (the specimens were all kept before anti-infection treatment). The results showed that the gram-negative bacteria were more sensitive to piperacillin of broad-spectrum penicillins, and generally resistant to ampicillin. For cephalosporins, except for the fourth-generation cefepime and the third-generation ceftazidime, gram-negative bacteria were generally resistant to the first, second, and third-generation cephalosporins, with an average resistance rate of 47%. The resistance rate of sulfonamides was close to 70%. It was generally sensitive to penicillin/cephalosporin + β -lactamase inhibitors, aminoglycosides, and carbopenems. Relatively sensitive to quinolones(Table 2).

Table 2
Resistance of Gram-negative bacteria isolates to antimicrobial agents

Types of Antimicrobial agent	Antimicrobial agent(s)	Total no. of isolates	Susceptible	Intermediate	Resistant	%Resistant
Penicillins	ampicillin	16	3	0	13	81.25
Cephalosporins	piperacillin	7	6	1	0	0
Penicillins	cefazolin	17	7	2	8	47.06
/ Cephalosporins	cefuroxime	16	8	0	8	50.00
+β-lactamase inhibitors	ceftriaxone	17	10	1	6	35.29
	ceftazidime	24	19	0	5	20.83
Carbopenems	cefepime	24	19	1	4	16.67
Aminoglycosides	ampicillin/sulbactam	17	11	2	4	23.53
Quinolones	cefoperazone/sulbactam	22	19	1	2	9.09
Tetracyclines	piperacillin/tazobactam	25	24	1	0	0
Sulfonamides	ticarcillin/clavulanicacid	23	17	3	3	13.04
Other	imipenem	24	23	1	0	0
	meropenem	22	22	0	0	0
	gentamicin	24	20	1	3	12.50
	amikacin	24	24	0	0	0
	tobramycin	9	9	0	0	0
	ciprofloxacin	24	14	0	10	41.67
	levofloxacin	24	14	5	5	20.83
	norfloxacin	7	7	0	0	0
	minocycline	16	15	0	1	6.25
	tigecycline	2	2	0	0	0
	cotrimoxazole	16	5	0	11	68.75
	chloramphenicol	15	9	1	5	33.33
	nitrofurantoin	17	14	1	2	11.76
	aztreonam	9	7	2	0	0
	cefoxitin	16	14	0	2	12.50

Risk Factors for Infection

The general characteristics of these patients, and the distribution of potential risk factors for infection, were shown in Table 3. There were significant differences in age, diseases duration, smoking, HB, WBC, CRP, ESR, IgA, IgG, IgM, albumin, corticosteroids, nonbiologic DMARDs and biological agents between the two groups ($P < 0.05$). Sex was not associated with risk of infection in the analyses. Some disease-related factors were not associated with infection risk (including

positive RF and CCP). Extraarticular manifestation,pulmonary interstitial disease ,was not associated with increased risk of infections. For the details of medication use,more than one-fifth of all patients21.3% received corticosteroids for long-term. Among all 138 patients with RA who had been treated with prednisone , except for 20 cases (14%)of prednisone whose dosage was 12.5±5 mg/day, the remaining 94 cases(68%) of prednisone were ≤7.5 mg/day, and 82 cases(59%) of prednisone were ≤5mg/Day.The patients who had been treated with low-dose corticosteroids for long term in this study were susceptible to infection . Among the 331 patients with RA treated with nonbiologic DMARDS , 249 patients were treated with MTX\HCQ\LEF\SSZ\AZA\CsA alone or in combination, and most of them were long-term low-dose applications. Methotrexate(MTX) had been prescribed for more than a quarter of the patients(26.3%).In addition, 17 patients were treated with cyclophosphamide at a maximum dose of 0.4g/week. 6 cases developed infections, including 3 cases of pneumonia, 2 cases of upper respiratory tract infection, and 1 case of skin herpes. They recovered after anti-infective treatment. Only 31(4.8%) of the patients had been treated with biologic therapy,of which 12, 12, and 7 cases of tocilizumab, Etanercept, and infliximab were respectively. A total of 2 cases resulted in infections, 1 case was chlamydial pneumonia caused by infliximab, and 1 case was urinary tract infection caused by tocilizumab. There were no special infections such as tuberculosis.

The factors that were associated with an increased in the risk of objectively confirmed infections in binary logistic regression model were shown in Table4,including higher age, long diseases duration, smoking, hypoproteinemia. Of the medications included in our analyses,use of corticosteroids was a strong and statistically significant predictor of infection(P<0.01). Use of nonbiologic DMARDS was negatively with infection.Use of biologics was difficult to assess,due to the small number of patients who took these medications.However ,the available data suggest that there was no increased risk of infection with use of biologics(Table4).

Table3 Relationship between baseline characteristics and infection in patients with RA

	Without infection(n=466)	With infection(n=182)	P
Age(years,mean±SD)	59±12	64.4±11.2	<0.01
Female,n(%)	363(78%)	142(78%)	0.972
Disease duration(years,mean±SD)	9.4±9.2	12±11.1	0.003
Smoke,n(%)	55(11.8%)	42(23.1%)	<0.01
Hb(g/L,mean±SD)	118±18.9	113.9±20	0.040
PLT(10 ¹² /L,mean±SD)	255.3±87.8	251.4±105.1	0.483
WBC(10 ⁹ /L,mean±SD)	6.4±2.1	8.1±4.5	<0.01
Albumin(g/L,mean±SD)	38.6±4.7	35.3±5.7	<0.01
CRP>10mg/L,n(%)	242(51.9%)	134(73.6%)	<0.01
ESR(mm,mean±SD)	35.6±20.4	43.2±21.4	<0.01
IgA(g/L,mean±SD)	3.1±1.2	3.4±1.2	<0.01
IgG(g/L,mean±SD)	13.8±3.9	13.3±4	0.048
IgM(g/L,mean±SD)	1.2±0.6	1.3±0.7	0.002
RF positive,n(%)	381(81.8%)	157(86.3%)	0.170
CCP positive,n(%)	412(88.4%)	166(91.2%)	0.303
C3(g/L,mean±SD)	1.2±0.2	1.2±0.2	0.539
C4(g/L,mean±SD)	0.3±0.08	0.3±0.2	0.084
Comorbidities,*n(%)	170(36.5%)	55(42.3%)	0.226
* Interstitial lung disease			
Medications,n(%)			
PSL(mg/day)	0.9±2.3	2.3±3.9	<0.01
PSL,any dose	82(17.6%)	66(36.3%)	<0.01
PSL≥5mg/day	59(12.7%)	50(27.5%)	<0.01
No DMARDs	215(46.1%)	102(56%)	0.023
MTX	68(14.6%)	19(10.4%)	0.163
Biologics	29(1.9%)	2(1.9%)	0.006
*n=596(excluded infected patients with non-pulmonary infections)			

Table4 Binary logistic regression analysis of risk factors for infection of RA patients

	b	SE	Wald	P	OR(95%CI)
Age≥65years	0.471	0.203	5.380	0.020	1.601(1.076-2.384)
Disease duration≥2years	0.886	0.304	8.469	0.004	2.425(1.335-4.404)
Smoke	0.626	0.261	5.767	0.016	1.871(1.122-3.119)
WBC	1.014	0.246	16.996	0.000	2.756(1.702-4.463)
CRP>10mg/L	0.648	0.238	7.392	0.007	1.911(1.198-3.049)
Albumin<30g/L	0.964	0.373	6.681	0.010	2.622(1.262-5.445)
PSL	1.053	0.236	19.884	0.000	2.866(1.804-4.554)
DMARDs	-0.592	0.214	7.648	0.006	0.553(0.363-0.842)
Biologic	-1.537	0.772	3.959	0.047	0.215(0.047-0.977)

Discussion

In this retrospective study, we showed the infection rate of RA patients, common infection sites and strains, and antimicrobial susceptibility results. In addition, we illustrated several factors that increase the risk of development of infection in RA patients.

In this study, the incidence of infection in the whole hospital (28.09%) was higher than that of the Department of Rheumatology and Immunology (19.15%), the reason was that some patients did not go to the Department of Rheumatology and Immunology because of severe infection symptoms but went to the corresponding department for anti-infection treatment. Our results suggested that the most frequent infection site in RA patients was the respiratory tract, accounting for more than half of all infections. *Pseudomonas aeruginosa* and *Staphylococcus aureus* were the main pathogens. The next most frequent infection site was the urinary tract, *Escherichia coli* was the main pathogen. The rates of infections and common infection sites in our study were similar to some studies [5–7]. In addition, several patients developed herpes, tuberculosis, and fungal infections. And the results of drug sensitivity showed that the proportion of resistant strains was relatively high. Therefore, in the process of diagnosis and treatment, we must be alert to the infection of the special pathogenic *Mycobacterium tuberculosis*. For patients with RA co-infection, antibiotics should be used rationally to avoid secondary fungal infections during anti-infection treatment.

We identified several factors that increased the risk of development of infection in RA patients. These included higher age, long diseases duration, smoking, hypoproteinemia. Of the medications included in our analyses, only corticosteroids increased infection risk. Use of nonbiologic DMARDs was negatively with infection. Biological agents did not increase the risk of infection. The results were consistent with some studies [6, 8–10, 2, 11–15]

Increasing age as an important risk factor for infections. Aging generally induces age-related immune dysfunction, leading to the increased incidence and severity of infections [15, 14].

A considerable exogenous risk factor for the development of infection was smoking. It was linked to the pathogenesis of RA and at the same time was a risk factor for infectious diseases [16, 17]. The significantly elevated serum levels of WBC and CRP were the detection indicators for whether the patient had infection.

A study showed that the DAS28 was slightly but significantly correlated with serum levels of IgA, IgG, IgM but not RF or anti-CCP [18]. In addition, one study had shown that each 0.6 unit increase in DAS28 score corresponded to a 4%

increased rate of outpatient infections and a 25% increased rate of infections requiring hospitalization[19]. One other study found no association between disease activity (DAS28) and infection rate[13]. In our study, statistically significant difference in IgA,IgG,IgM between the infected group and the non-infected group was not observed. Whether IgA, IgG, IgM are related to infection in patients with RA still needs further research.

Corticosteroids are potent immune suppressive drugs that are widely used in rheumatological care. In our study, patients who had been treated with low-dose corticosteroids for long term in this study were susceptible to infection. Previous studies revealed no increase in infection risk of RA with corticosteroids at a low dosage[20–22]. Considering the time-dependent and dose-dependent of the side effects of corticosteroids, corticosteroids should be actively and rationally used to control the condition when necessary.

Our research results indicated that use of nonbiologic DMARDs did not increase the risk of infection in RA, on the contrary, it reduced the risk of infection, similar to the results of some studies, the results suggested that methotrexate (MTX) and hydroxychloroquine (HCQ) were associated with a decreased risk; whereas for sulfasalazine (SSZ), leflunomide (LEF), azathioprine (AZA), cyclosporine A (CsA) and other nonbiologic DMARDs there was no association[6]. Use of nonbiologic DMARDs was associated with a small decrease in mild infection risk and not associated with increased serious infection risk[9]. The reason for the findings was not known but may relate to a beneficial effect of controlling RA inflammation, counterbalancing the potential immunosuppressive effects of nonbiologic DMARDs and resulting in a net neutral effect on infections[9]. Patients taking nonbiologic DMARDs are likely to have been taking those drugs for a period of time, and the patients who continued to receive therapy during this study period may have had a lower risk for adverse events such as infections related to those medications[6].

MTX is an immunosuppressive non-biologic DMARD, which is used as a first-line drug for the treatment of RA[23, 24]. Some studies had also shown that long-term use of MTX did not appear to be a risk factor for infections in RA patients [8, 9, 25, 26]. Whether MTX contributes to increased susceptibility to infection is still controversial. An increased risk with methotrexate compared with other DMARDs was found in some studies[27, 28, 7, 6, 29].

Biologics play an important role in the treatment of RA and provide substantial benefit to many RA patients in controlling disease symptoms and progression, especially in patients whose disease is not responding to treatment with conventional DMARDs. However, biologic agents, due to their immunologic properties, are assumed to be contributing to the increased susceptibility to infection in RA. Previous studies had reported that biologic agents increased the risk of infection in RA patients[30–32]. There was conflicting information regarding the increased risk for infection with biological. We found no evidence of an increased risk of infections associated with biologics, which was consistent with the findings of some others[26, 12, 13]. A recent research of infection risk performed using the German biologics register RABBIT may help to explain these conflicting reports[33]. An increased risk of infection during the first year of treatment with biologics was found, with a subsequent decline in infection risk due to improvement in disease activity, reduction in concomitant corticosteroid use and discontinuation of biologics among patients with high risk of infections. In addition, previous studies had shown that biologics increased the incidence of opportunistic infections such as tuberculosis in RA patients [34, 35]. However, we had not found any patients with tuberculosis infection caused by the use of biological agents. In our study, biologics were assessed and appeared to confer no increased risk of infections, but these associations did not reach statistical significance due to low prevalence of use of these medications.

Pulmonary interstitial disease is one of the most common comorbidities in patients with RA. In this study, after excluded infected patients with non-pulmonary infections, the chi-square test showed no statistical significance ($P=0.226$). The results were inconsistent with some studies[8, 10, 11], which may be related to the degree of pulmonary interstitial lesions.

This study was retrospective analysis and had several limitations. The overall number of cases was low, the strains in the drug susceptibility test of patients with RA co-infection were too low. Another limitation was that we were not able to quantify the dose of the therapeutic drugs. Information about comorbidities such as diabetes mellitus and cardiac disorders, and other chronic diseases were not available.

Conclusions

In conclusion, the common infection sites in patients with RA are the respiratory tract and urinary tract..Gram-negative bacteria are common pathogens. Patients with higher age, long diseases duration, hypoproteinemia, long-term smoking and corticosteroid therapy are more susceptible to infection. These results advance our understanding of the relationship between infections and RA, and may help to prospectively identify high-risk patients,For patients with RA co-infection, antibacterial drugs should be carefully selected based on the results of drug sensitivity.

List Of Abbreviations

Abbreviation	Full Title
RA	Rheumatoid arthritis
Hb	Hemoglobin
PLT	Blood platelet
WBC	White blood cell
CRP	C-reactive protein
ESR	Erythrocytesedimentation rate
C3	Complement3
C4	Complement4
IgA	ImmunoglobulinA
IgG	ImmunoglobulinG
IgM	ImmunoglobulinM
RF	Rheumatoid factor
Anti-CCP	Anti-citrullinepolypeptideantibody
CTX	Cyclophosphamide
DMARDS	Disease-modifying antirheumatic drug

Declarations

Ethics approval and consent to participate: The study involving human participants were reviewed and approved by Ethics Committee of Fourth Affiliated Hospital of China Medical University and General Hospital of Northern Theater Command; there was no requirement for individual patient consent because the project did not impact clinical care and all protected health information was deidentified.

Consent for publication: All authors agree to publish.

Availability of data and materials: The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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References

1. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum.* 2002;46(9):2287-93. 'doi':10.1002/art.10524.
2. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. *Rheumatology (Oxford).* 2013;52(1):53-61. 'doi':10.1093/rheumatology/kes305.
3. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CR et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *ANN RHEUM DIS.* 2010;69(9):1580-8. 'doi':10.1136/ard.2010.138461.
4. Nosocomial infection diagnostic criteria (trial implementation). *Chinese Medical Journal.* 2001(05):61–7
5. Kawashima H, Kagami SI, Kashiwakuma D, Takahashi K, Yokota M, Furuta S et al. Long-term use of biologic agents does not increase the risk of serious infections in elderly patients with rheumatoid arthritis. *RHEUMATOL INT.* 2017;37(3):369-76. 'doi':10.1007/s00296-016-3631-z.
6. Smitten AL, Choi HK, Hochberg MC, Suissa S, Simon TA, Testa MA et al. The risk of hospitalized infection in patients with rheumatoid arthritis. *J RHEUMATOL.* 2008;35(3):387–93
7. Au K, Reed G, Curtis JR, Kremer JM, Greenberg JD, Strand V et al. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. *ANN RHEUM DIS.* 2011;70(5):785-91. 'doi':10.1136/ard.2010.128637.
8. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. *Arthritis Rheum.* 2002;46(9):2294-300. 'doi':10.1002/art.10529.
9. Lacaille D, Guh DP, Abrahamowicz M, Anis AH, Esdaile JM. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. *Arthritis Rheum.* 2008;59(8):1074-81. 'doi':10.1002/art.23913.
10. Hashimoto A, Suto S, Horie K, Fukuda H, Nogi S, Iwata K et al. Incidence and Risk Factors for Infections Requiring Hospitalization, Including Pneumocystis Pneumonia, in Japanese Patients with Rheumatoid Arthritis. *Int J Rheumatol.* 2017;2017:6730812. 'doi':10.1155/2017/6730812.
11. Crowson CS, Hoganson DD, Fitz-Gibbon PD, Matteson EL. Development and validation of a risk score for serious infection in patients with rheumatoid arthritis. *Arthritis Rheum.* 2012;64(9):2847-55. 'doi':10.1002/art.34530.
12. Grijalva CG, Chen L, Delzell E, Baddley JW, Beukelman T, Winthrop KL et al. Initiation of tumor necrosis factor-alpha antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. *JAMA.* 2011;306(21):2331-9. 'doi':10.1001/jama.2011.1692.

13. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum.* 2006;54(8):2368-76. 'doi':10.1002/art.21978.
14. Gavazzi G, Krause KH. Ageing and infection. *LANCET INFECT DIS.* 2002;2(11):659-66. 'doi':10.1016/s1473-3099(02)00437-1.
15. Grubeck-Loebenstein B, Berger P, Saurwein-Teissl M, Zisterer K, Wick G. No immunity for the elderly. *NAT MED.* 1998;4(8):870. 'doi':10.1038/nm0898-870b.
16. Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum.* 2006;54(1):38-46. 'doi':10.1002/art.21575.
17. Stampfli MR, Anderson GP. How cigarette smoke skews immune responses to promote infection, lung disease and cancer. *NAT REV IMMUNOL.* 2009;9(5):377-84. 'doi':10.1038/nri2530.
18. Gottenberg JE, Miceli-Richard C, Ducot B, Goupille P, Combe B, Mariette X. Markers of B-lymphocyte activation are elevated in patients with early rheumatoid arthritis and correlated with disease activity in the ESPOIR cohort. *ARTHRITIS RES THER.* 2009;11(4):R114. 'doi':10.1186/ar2773.
19. Au K, Reed G, Curtis JR, Kremer JM, Greenberg JD, Strand V et al. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. *ANN RHEUM DIS.* 2011;70(5):785-91. 'doi':10.1136/ard.2010.128637.
20. Roubille C, Rincheval N, Dougados M, Flipo RM, Daures JP, Combe B. Seven-year tolerability profile of glucocorticoids use in early rheumatoid arthritis: data from the ESPOIR cohort. *ANN RHEUM DIS.* 2017;76(11):1797-802. 'doi':10.1136/annrheumdis-2016-210135.
21. Strehl C, Bijlsma JW, de Wit M, Boers M, Caeyers N, Cutolo M et al. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force. *ANN RHEUM DIS.* 2016;75(6):952-7. 'doi':10.1136/annrheumdis-2015-208916.
22. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis.* 1989;11(6):954-63. 'doi':10.1093/clinids/11.6.954.
23. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2012;64(5):625-39. 'doi':10.1002/acr.21641.
24. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *ANN RHEUM DIS.* 2014;73(3):492-509. 'doi':10.1136/annrheumdis-2013-204573.
25. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. *ANN RHEUM DIS.* 2009;68(7):1100-4. 'doi':10.1136/ard.2008.093690.
26. Crowson CS, Hoganson DD, Fitz-Gibbon PD, Matteson EL. Development and validation of a risk score for serious infection in patients with rheumatoid arthritis. *Arthritis Rheum.* 2012;64(9):2847-55. 'doi':10.1002/art.34530.
27. Greenberg JD, Reed G, Kremer JM, Tindall E, Kavanaugh A, Zheng C et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. *ANN RHEUM DIS.* 2010;69(2):380-6. 'doi':10.1136/ard.2008.089276.
28. van der Veen MJ, van der Heide A, Kruize AA, Bijlsma JW. Infection rate and use of antibiotics in patients with rheumatoid arthritis treated with methotrexate. *ANN RHEUM DIS.* 1994;53(4):224-8. 'doi':10.1136/ard.53.4.224.

29. Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis. *Rheumatology (Oxford)*. 2007;46(7):1157-60. 'doi':10.1093/rheumatology/kem076.
30. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology (Oxford)*. 2011;50(1):124-31. 'doi':10.1093/rheumatology/keq242.
31. Curtis JR, Patkar N, Xie A, Martin C, Allison JJ, Saag M et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. *Arthritis Rheum*. 2007;56(4):1125-33. 'doi':10.1002/art.22504.
32. Listing J, Strangfeld A, Kary S, Rau R, von Hinueber U, Stoyanova-Scholz M et al. Infections in patients with rheumatoid arthritis treated with biologic agents. *Arthritis Rheum*. 2005;52(11):3403-12. 'doi':10.1002/art.21386.
33. Strangfeld A, Eveslage M, Schneider M, Bergerhausen HJ, Klopsch T, Zink A et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? *ANN RHEUM DIS*. 2011;70(11):1914-20. 'doi':10.1136/ard.2011.151043.
34. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med*. 2001;345(15):1098-104. 'doi':10.1056/NEJMoa011110.
35. Takeuchi T, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. *ANN RHEUM DIS*. 2008;67(2):189-94. 'doi':10.1136/ard.2007.072967.