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Review Article

Legionnaires' Disease and Use of Tumor Necrosis Factor-Alpha Inhibitors: A Forthcoming Problem?

Zorica Nanovic[1*], Milena Petrovska[2]

[1]Institute of Lung Diseases and Tuberculosis, Vodnjanska 17, Skopje 1109, Republic of Macedonia; [2]Institute of Microbiology and Parasitology, Medical Faculty, University Ss Cyril and Methodius of Skopje, Republic of Macedonia

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Key words: opportunistic infection; Legionnaires' disease; TNF-α inhibitors; immunosuppresion; rheumatic diseases.

[*]**Correspondence:** Dr. Zorica Risto Nanovic. Institute of Lung Deseases and Tuberculosis, Vodnjanska 17, Skopje 1109, Republic of Macedonia. Phone: + 389 2 3229 166. Fax: + 389 2 3229 166. E-Mail: znanovic@hotmail.com

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Abstract

Aim: To establish a review in the current literature and to analyze the relation Legionnaires' disease – TNF-α inhibitors, in order to estimate the real indications for such connection.

Material and Methods: The electronic data for PubMed and Google Scholar have been searched, according to the vocabulary: legionellosis, epidemiology, outbreak, diagnosis, pathogenesis, therapy, TNF-α inhibitors, indications, side effects, risk of infection. The obtained studies have been selected in English, according to the relevance by the topic.

Results: Selected papers, consisted of ten studies and eight case reports, yielded 35 cases of Legionnaires' disease associated with the use of TNF- α inhibitor treatment.

Discussion: There is a prevailing conclusion for increased risk of serious infections while using TNF-α inhibitors and also a deficiency of studies for an association of Legionnaires' disease with the use of TNF-α inhibitors. Sub-diagnosing and no-existence of screening before the anti-TNF-α therapy blur the factual profile for the researched relation. The possibility for latent infection has not been sufficiently researched.

Conclusion: There are indications that Legionnaires' disease in the therapy with TNF-α inhibitors is indeed a forthcoming problem. Additional target researches are required in order to establish the position of Legionnaires' disease in the mosaic of anti - TNF-α therapy.

Introduction

The introduction of a novel class of drugs named "biological agents" more than a decade ago, was followed by period of uprising concern regarding their safety profile. In spite of the revolutionary role in the treatment of broad spectrum of inflammatory diseases, it has to be considered that several significant side effects might seriously compromise the use of these drugs, including the increased probability of acquiring an opportunistic infection.

Bacteria from the species *Legionella* were included in the microbiological taxonomy in 1977, after the first registered outbreak of Legionnaires' disease in the United States of America in 1976 [1]. Genetic, phenotypc and antigenic characteristics are described elsewhere [2, 3], as well as microbiological diagnostic procedures [4]. 91.5% of legionellosis cases are caused by bacteria belonging to the genus of *L. pneumophila*, and *Legionella pneumophila* serogroup 1 is of crucial importance for human infection, being responsible for 84.2% of legionellosis cases [5].

Legionellas are primarily found around fresh water environments (such as lakes and streams) in the nature. Natural reservoirs of fresh water are not reservoirs of legionellosis outbreaks. In man-made water pipe systems, the largest number of *legionella* is sessile and survives within biofilms. *L. pneumophila* multiplies at temperatures between 25 ^{o}C and 42^{o}C, with an optimal growth temperature of 35^{o}C [4]. Humans are infected by inhalation of *legionella*-contaminated aerosols, and the source of these aerosols might be different including: taps, showers, air-conditioning systems, hospital respiratory therapy

devices, spa or natural pools, water fountains, etc. [6]. Owing to the unique virulence traits, the bacterium survives and is replicated intracellularly, being previously phagocytosied by alveolar macrophages [3].

Legionella is an opportunistic pathogen since in healthy humans the infection is self-limiting and these individuals may remain asymptomatic. Risk factors associated with *legionella* infection include: older age, male gender, smoking status, chronic diseases with or without immunosuppression [6].

Legionellosis usually occurs sporadically, and sometimes in outbreaks. It is most frequently manifested as pneumonia (the so-called Legionnaires' disease), which is often severe, or as the so-called Pontiac fever (flu-like illness) [7]. Newer generation of macrolides and azalides (clarithromycin, azithromycin) and fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) has been shown to penetrate rapidly and achieve a high level of concentration in phagocytic cells [8], an attribute that makes them drugs of choice in Legionnaires' disease.

Legionella spp. is one of the most common causative agents of community-acquired pneumonia (CAP): 2-15% of all hospitalized patients for CAP in Europe and North America are caused by *Legionella* [7], and recent studies suggest an increasing rate of legionellosis cases [9]. *Legionella spp.* has been isolated with variable incidence (1-40%) in hospital-acquired pneumonia (HAP), which has a significantly higher mortality rate than CAP (up to 40%) [10]. Mortality rate due to *Legionella* pneumonia is still high although since 1990 it has a decreasing tendency, from 26% to 10% for CAP [11].

Tumor necrosis factor-α (TNF-α) is a pro-inflammatory cytokine, which plays a critical role in the pathogenesis of different inflammatory and/or immunologically-conditioned diseases [12]. TNF-α inhibitors are biological agents that specifically target this key of inflammation cascade, prevent binding to its receptors and thus block its effect. Since the introduction of the first TNF-α inhibitor – infliximab – in the therapy of rheumatoid arthritis (RA) in 1999 [13] until today, two other drugs of the same group have also been approved – adalimumab and etanercept, and the indications have been expanded on other chronic inflammatory/immunologic diseases, both rheumatologic and non-rheumatologic ones [14, 15]. Infliximab and adalimumab are anti-TNF-α monoclonal antibodies, which bind with high affinity to human TNF-α and neutralize its biological activity. Etanercept is a fusion protein, which acts as a soluble receptor and is competitively bound to TNF-α.

TNF-α also plays an important role in host immune response to infectious pathogens [10, 16], being a critical component of both anti-bacterial protective and anti-inflammatory response to infections, especially with intracellular viable microorganisms.

The role of TNF-α and cell-mediated immunity in the organism defence from *L. pneumophila* has been well acknowledged and documented [17]. TNF-α plays a key role in the inhibition of bacterial growth and replication, and resolution of *Legionella* pneumonia [18, 19]. This observation has been supported by the relative Th1-cytokine profile predominance in patients with Legionnaires' disease [20].

Interference with the function of TNF-α with a subsequent reduction of tissue levels of bioactive TNF-α is beneficial for patients suffering from RA or similar diseases, but it raises the question of continual supply of effector cells in the infectious loci, thus compromising the cell-mediated immunity to intracellular microorganisms (including *L. pneumophila*). In this manner, TNF-α suppression is a double-edged sword: by reducing TNF-α high levels the inflammation is reduced, but low levels of biologically active TNF-α might be associated with an increased risk for infections, especially with opportunistic microorganisms.

In spite of the relatively secure safe profile, derived from the phase III of clinical trials [21], lately a large number of post-marketing studies report on the increased incidence/risk from infection when using these agents. Many of them are focused on tuberculosis while the remaining "rarer" opportunistic pathogens, including *legionella*, are hardly ever subject to observation.

The incidence of *Legionella* pneumonia in immunocompromised patients as well as in patients receiving anti-TNF-α therapy has not been identified [10]. The aim of this study was, based on the available literature data, to analyze the relationship between Legionnaires' disease and TNF-α inhibitors, to assess whether indices for this relationship are real, and depending on the findings gathered - to suggest future activities.

Material and Methods

To accomplish the aim of this review paper, a systematic literature search covering the period between 01.01.1977 and 01.02.2013 was performed using PubMed and Google Scholar electronic databases, to identify all relevant articles (i.e. articles reporting the exact cases of *Legionella* pneumonia during TNF- α inhibitor treatment). The search was limited to full text English language papers, using the following key words: legionellosis, epidemiology, epidemiological investigation, outbreak, diagnosis, pathogenesis, therapy, biological agents, TNF-α, TNF-α inhibitors, TNF-α blockers, TNF-α antagonists, anti-TNF-α therapy, indications, side effects, risk of infection.

Results

Selected papers can be divided into case reports and studies, both observational and interventional. Case reports presented patients who experienced Legionnaires' disease while receiving anti-TNF-α therapy for Behcet's and Chron's desease, psoriasis and RA [10, 22-28]. The results of the studies are as follows:

The retropective study of Kroesen et al. (2003) was conducted in 60 patients with RA treated with etanercept or infliximab. Serious bacterial infections (including one case of *Legionella* pneumonia) were registered in 11 (18.3%), the incidence being 0.181 per TNF-α treatment year vs. 0.008 per year without treatment in the 2 years preceding anti-TNF-α therapy [29].

In the prospective observational cohort study of 7,664 anti-TNF-α treated and 1,354 DMARD-treated patients with severe RA from the British Society for Rheumatology Biologics Register (BSRBR), Dixon et al. (2006) reported that anti-TNF-α therapy was not associated with an increased risk of overall serious infections compared to non-biological DMARDs treatment, nor there was a difference in the risk among the three used TNF-α inhibitors. However, they reported an increased risk of bacterial intracellular infections among patients treated with TNF-α inhibitor: of 525 episodes of serious infections in TNF- α inhbitor treated cohort, 19 were bacterial intracellular including 2 cases of *Legionella* pneumonia. No bacterial intracellular infection was registered in the DMARD-treated cohort [30].

The retrospective observational study of Curtis et al. (2011) was conducted in 6992 RA patients registered at large US healthcare organization and treated with different biological agents. It reported hospitalized infection rates in patients who were treated for the first time with a TNF-α inhibitor (infliximab, adalimumab, etanercept) or other biological agent (rituximab and abatacept) and in "switchers" from one to another biological agent of 4.6 and 7.0 per 100 patient-years, respectively ($p<0.0001$); the highest rate was registered for infliximab in both groups. Among 364 hospitalized infections, the majority of 124 (23,7%) were due to pneumonia (with no causative organism indicated), while 23 (including two cases of *Legionella* pneumonia) were due to "specific site/type of infection" [31].

By analyzing the RATIO Registry (Recherche Axée sur la Tolérance des Biothérapies), designed to collect data on opportunistic and severe infections in patients treated with TNF-α inhibitors, Tubach et al.reported 10 cases of *L. pneumophila* pneumonia in France during 2004, with an overall legionellosis incidence rate in France of 2/100 000 and *L. pneumophila* infection incidence rate of 33-42/100 000 in patients treated with TNF-α inhibitors. In one of these 10 patients, re-introduction of infliximab was followed by second episode of Legionnaires' disease. Only one case of legionellosis in a patient with RA not treated with TNF-α inhibitors was reported during the same period [32].

Goekoop-Ruiterman et al. (2007) conducted a randomized controlled clinical trial in 508 patients, designed to compare the clinical and radiographic efficacy of four different therapeutic approaches for RA, with infliximab included (in different way) in each of them. 10 patients (8%) from group 1 experienced infection, including one case of *Legionella* pneumonia [33].

By analyzing the Spanish BIOBADASER registry (a national drug safety registry of patients with rheumatic diseases) Pérez-Sola et al. (2011) reported 907 episodes of infection in 706 (10%) out of 6,969 patients. Among 101 (11.1%) episodes of pneumonia, 25 (24%) were with confirmed etiology, *Legonella spp.* being causative agent in 5 (including 1 fatal) cases. The overall infection incidence rate was 53.09/1,000 patients-years (CI 95%; 49.69-56.66) and pneumonia incidence rate was 5.97/1,000 patients-years (CI 95%; 4.87-7.25) [34].

The study of Kohn et al. (2007), conducted to evaluate short- and long-term effectiveness and safety of infliximab in 83 patients (46 analyzed retrospectively and 37 prospectively) with severe refractory ulcerative colitis, reported infection as an adverse event in 5 patients (6%), including one case of fatal *Legionella* pneumonia [35].

The study of Aringer et al. (2009) was conducted to examine the adverse events and efficacy of infliximab during the long-term follow up of 13 patients with systemic lups erythematodes (6 included in an open-label trial, and 7 treated on an individual compassionate care basis after standard therapy had failed). Short-term and long-term treatment revealed infection complications in 5 and 2 patients (including one case of fatal *Legionella* pneumonia), respectively [36].

Panaccione et al. (2011) conducted a phase III open-label study to examine the efficacy and safety of adalimumab in 304 Canadian patients with moderate to severe Crohn's disease (ACCESS trial). Eight patients (2.6%) experienced serious infections, including *Legionella* pneumonia in one patient [37].

The retrospective study of Favalli et al. (2008) was conducted in terms of examination of pattern of utilization and the costs of therapy of infliximab, in 95 patients with refractory RA. During the observational period of one year, the sole adverse event was *Legionella* pneumonia in one patient (1.05%) [38].

Cases of *Legionella* pneumonia associated with TNF-α inhibitor therapy are compiled in Table 1. Important thing to notice is partial or complete lack of relevant clinical data in 13 out of 35 reported cases, mainly in the large studies (exception is the of study of

Table 1: Clinical features of the patients with Tumor necrosis factor - α inhibitor – associated Legionnaires' disease.

Source	Age /sex	Indication	Disease duration	Co - morbidities	TNF-α inhibitor	Treatment duration	Concomitant immunosupressive therapy	Infection origin	Clinical/ radiological features	Diagnostic modality	Antibiotic therapy	Outcome
Beigel et al. [10]	58/M	CD	12 m.	Smoker	IFMB	N/A	Azathioprine, mesalazine, prednisolone	C	ULP, respiratory failure	PCR (+) BAL (LP1); LPAg (+) (LP1)	Moxifloxacin	ICU admission. Recovered.
Mancini et al. [22]	30/M	Behçet's disease	8 y.	Pulmonary TB	IFMB	4 w.	MTX	C	ULP, pleural effusion**	LPAg (+) (LP1)	Levofloxacin + Rifampicin	Recovered
Hofmann et al. [23]	26/M	CD	2 m.	Smoker	IFMB	4 w.	6-mercaptopurine, prednisone	N	BLP, ARDS**.	LPAg (+) (LP1)	Azithromycin	ICU admission, Recovered
	59/M	CD	4 m.	Smoker, COPD	IFMB	4 w.	Methyl-prednisolone	N	BLP, lung abscess, ARDS	LPAg (+) (LP1)	Azithromycin	ICU admission. Died.
Christidis et al. [24]	55/M	RA	N/A	Smoker	IFMB	49 w.	Prednisolone, cyclosporine A, MTX	N/A	BLP, lung cavitation	LPAg (+) (LP1); serology (titer 1:512)	Clarithromycin + Rifampicin	Recovered
Jinno et al. [25]	67/F	RA	N/A	Smoker	ALMB	2 y.	MTX	C	ULP, pleural effusion	PCR&DFA (+) BAL; LPAg (+) (LP1)	Moxifloxacin + Rifampicin	ICU admission. Recovered
Wuerz et al. [26]	67/F	RA	>2 y.	Hypothyroidism	ALMB	10 w.	Azathioprine	C	ULP, PE, lung cavitation**	Culture (+) BAL; LPAg (+) (LP1)	Levofloxacin + Rifampicin, Azithromycin	ICU admission, Recovered
Porzio et al. [27]	42/M	Psoriasis	N/A	N/A	IFMB	9 m.	MTX	N/A	BLP, lung cavitation, pleural effusion**	PCR (+) BAL, LPAg (+) (LP1)	Levofloxacin + Azithromycin	Recovered
Epping et al. [28]	26/F	CD	2 y.	Pregnancy (6th month)	IFMB	58 w.	None	C	ULP**	L.*pneum.* (+) IgM and IgG; LPAg (+) (LP1)	Erythromycin	Recovered
Kroesen et al. [29]	49/M	RA	> 7 y.	Psoriasis	IFX	N/A	MTX	N/A	BLP	LPAg (+) (LP1)	N/A	N/A
Dixon et al. [30]	59/M	RA	N/A	N/A	IFX	32 m.	N/A	N/A	LRTI	N/A	N/A	N/A
	49/M	RA	N/A	N/A	IFX	4 m.	N/A	N/A	LRTI	N/A	N/A	N/A
Curtis et al. [31]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	43/M	RA	N/A	Diabetes mellitus	ALMB	71 w.	MTX, prednisone	C	BLP**	LPAg (+) (LP1)	FLQ	Recovered
	55/F	RA	30 y.	No	ALMB	26 w.	MTX , prednisone	C	ULP	LPAg (+) (LP1)	Macrolide, Rifampicin	Recovered
	67/M	RA	3,5 y.	Smoker; COPD	ETCP	16 w.	MTX, prednisolone	C	ULP, ARDS**	BAL culture (+); LPAg (+) (LP1)	Rifampicin, FLQ	ICU admission. Recovered
	46/F	Pyoderma gangrenosum	1,5 y.	Primary thrombocythemia	IFMB	73 w.	Prednisone, pipobroman	C	BLP, pleural effusion, ARDS**	LPAg (+) (LP1)	Macrolide, Rifampicin	ICU admission.
	58/M	Psoriasis	45 y.	Smoker	IFMB	3 w.	None	C	ULP, pleural Effusion	LPAg (+); PCR (+) sputum (LP1)	Macrolide, FQL	Recovered
Tubach et al. [32]	40/M	RA	4 y.	Diabetes mellitus, smoker; COPD	ALMB	34 w.	Sulfasalazine, betamethasone	C	ULP**	LPAg (+) (LP1)	Rifampicin, FLQ	Recovered
	45/F	RA	33 y.	Smoker	ALMB	36 w.	MTX, prednisone	C	ULP**	LPAg (+) (LP1)	Macrolide, FLQ	Recovered
	66/F	RA	10 y.	None	ALMB	45 w.	MTX	C	BLP, ARDS**	LPAg (-); seroconversion 1:16 ⇨ 1:256 (LP6)	FLQ, ceftriaxone	Recovered
	47/M	RA	3 y.	Smoker, water cleaning system worker	ALMB	50 w.	Prednisone	C	BLP, ARDS, pneumothorax	LPAg (+); BAL culture (+) (LP1)	Rifampicin, FLQ	ICU admission, Recovered
	69/F	RA	10 y.	None	ETCP^	45 w.	MTX, prednisone	C	BLP**	LPAg (+) (LP1)	FLQ	Recovered
	27/F	CD	5 y.	None	IFMB	1 w.	Azathioprine , prednisone	C	ULP, ARDS	LPAg (+); BAL culture (+)(LP1)	Rifampicin, FLQ	ICU admission. Recovered
Goekoop Ruiterman et al. [33]	N/A	RA	N/A	N/A	N/A	N/A	N/A	N/A	Pneumonia	N/A	N/A	N/A
Peŕez-Sola et al. [34]*	N/A	N/A	N/A	N/A	N/A	Median = 28 (6-45) m.	N/A	N/A	Pneumonia	N/A	N/A	Died/ N/A
Kohn et al. [35]	71/M	UC	2 y.	N/A	IFMB	11 d.	Glucocorticoids, mesalazine	N/A	Pneumonia, lung abscess**	PCR (+) sputum (LP1)	N/A	Died
Aringer et al. [36]	N/A	SLE	N/A	N/A	IFMB	12 m.	N/A	C	Pneumonia	N/A	N/A	ICU admission. Died.
Panaccione et al. [37]	N/A	CD	N/A	N/A	ALMB	N/A	N/A	N/A	Pneumonia	N/A	N/A	N/A
Favalli et al. [38]	N/A	RA	N/A	N/A	IFMB	N/A	N/A	N/A	Pneumonia	N/A	N/A	N/A

Abbreviations: ALMB=adalimumab; ARDS=acute respiratory distress syndrome; BLP=bilateral pneumonia; BAL=bronchoalveolar lavage; CD=Chron's disease; COPD= chronic obstructive pulmonary disease; C=community acquired pneumonia; d=day; ETCP=etanercept; F= female; FLQ=fluoroquinolone; IFMB=infliximab; ICU=intensive care unit; LRTI=low respiratory tract infection; LP1=*Legionella pneumophylla* serogroup1; LP6=*Legionella pneumophylla* serogroup 6; LPAg=*Legionella pneumophylla* urinary antigen; MTX=metotrexate; M= male; m=month; N= nosocomial pneumonia; N/A= information not available; PE=pulmonary embolism;PCR=polymerase chain reaction; RA=rheumatoid arthritis; SLE=systemic lupus erythematodes UC=ulcerative colitis;ULP=unilateral pneumonia; y=year; *Five patients share identical clinical findings, with exception of the outcome (one died; for other not available).; **Presence of clinical features beside respiratory system; ^ This patient experienced previous treatment with infliximab.

Tubach et al.[32]). The remaining reported cases are characterized with: (1) predominance of infliximab and adalimumab treated patients (25/27 patients); (2) high ICU admission rate (10/23 patients, i.e. 43.47%) and high mortality rate (4/23 patients, i.e.17.39%); (3) frequent concomitant therapy with other immunosuppressive drugs (20/22 patients), and co-morbidities (16/20 patients); (4) accompanying pleural effusion (5/22 patients) and pulmonary cavitations (5/22 patients). The case of *Legionella* pneumonia in a pregnant woman receiving TNF-α inhibitor [28] is particularly intriguing, having in mind that a patient with three concomitant immunomodulatory conditions (pregnancy, Crohn's disease and TNF-α inhibitor therapy) experienced quite a mild form of the disease, with full recovery under erythromycin therapy and giving birth to a healthy child.

Discussion

While reviewing the literature, one can notice that majority of studies suggest existence of an increased risk of serious infections (i.e. infection that led to hospitalization, death or required intravenous antibiotic treatment [30]) in patients treated with TNF-α inhibitors, especially of those caused by intracellular microorganisms, without focusing on Legionnaires' disease as a separate entity. Therefore, *L. pneumophila* infections are rarely described in patients receiving such therapy [32]. The study of Tubach et al. specifically analyzes development of Legionnaires' disease in patients receiving TNF-α therapy. A striking fact revealed from RATIO registry [32] is the large discrepancy between the overall legionellosis incidence rate in France in 2004 (2/100 000) and *L. pneumophila* infection incidence rate in patients treated with TNF-α inhibitors in the same year (33-42/100 000). The relative risk of 16.5-21 in this treated population compared to the relative risk in general population of France indirectly confirms the role of TNF-α in *L. pneumophila* infection. It is obvious that the probability for Legionnaires' disease development in patients receiving treatment with TNF-α inhibitors is greater than the overall risk in the general population in France. However, the influence of the disordered immunologic milieu on risk increasing is not to be neglected. In order to obtain conclusive data, the *L. pneumophila* infection rate has to be compared in patients receiving *vs.* patients not receiving TNF-α inhibitor (i.e. receiving non-biological DMARDs or placebo), who suffer from the same disease with same severity, and have no co-morbidities and no concurrent immunosupressive treatment. Unfortunately, there is a lack of such data.

An intriguing issue in this study is the appearance of second episode of confirmed Legionnaires' disease (without differentiation weather it was a relapse or a new exogenous infection) in one of the ten patients with Legionnaires' disease, following the re-introducing of treatment with infliximab [32]. Having in mind the reoccurrence of antigenuria with a concomitant negative culture and PCR finding from lower airways secretions in this patient, it is inevitable to think of the hypothetic possibility of a "dormant" state of the bacteria after the first contact with the host, with reactivation of endogenous infection after repeated use of TNF-α inhibitor, that actually re-established the state of immunosuppression. To date, the possibilities of development of a latent infection with intracellular *legionella* has not been thoroughly investigated nor were presented such a data in the literature. Additional research is necessary since existence of such a state of the bacterium might have implications on the therapy and prophylaxis of the disease.

It is a well-known fact that there is an increased risk for tuberculosis development in patients receiving anti-TNF-α therapy, as well as an existence of latent infection with this intracellular bacterium [16, 39]. Numerous reports on the association of tuberculosis and the usage of these therapeutic agents have resulted in international recommendations that impose screening for tuberculosis before initiation of TNF-α inhibitor therapy [14]. There is no such established screening protocol for the other intracellular pathogens, including *L. pneumophila* [10, 32]. Achieving consensus on the topic of screening will no doubt need a longer period, since conditioned by fulfilment of the following prerequisites to overcome under-diagnosis of Legionnaires' disease:

1. Enhancing availability of diagnostic tools. The two crucial diagnostic procedures (i.e. culture confirmation and PCR) are expensive, requiring sophisticated equipment and professional skills, and so affordable in few laboratories worldwide [4].

2. Providing detailed guidance for management of *Legionella* pneumonia. Current guidelines of European Respiratory Society [40] and American Thoracic Society/Infectious Disease Society of America [41] recommend testing on *Legionella* primarily in immunocompetent hospitalized patient in whom clinical or epidemiological suspicion for this infection emerges, considering the outpatient testing as "optional". In practice, *Legionella* pneumonia is radiographically and clinically indistinguishable from other forms of pneumonia [42], does not always have a severe clinical presentation requiring hospital treatment [43] and outpatient testing is rarely performed. Since there is a lack of precise guidelines, suspicion of Legionnaires' disease in patients receiving treatment with TNF-α inhibitor relies on subjective assessment of the physician who monitors the therapeutic response.

3. Improvement of passive and awkward disease-reporting networks [9]. Collected epidemiological data on Legionnaires' disease do not

refer to the real situation and underestimate the size of the problem. In favour of this statement speaks the discrepancy between the registered incidence and the estimated number of cases with Legionnaires' disease [9, 10, 43].

The need to overcome the problem of under-diagnosed Legionnaires' disease should not marginalize contemplation over introduction of screening test for *L. pneumophila* in patients – candidates for therapy with TNF-α inhibitor. A feasible solution, in lack of exact testing opportunity, might be detection of soluble *legionella* antigens in urine samples. The method is simple, rapid, cheap, and widely available, with high specificity and satisfactory sensitivity. Its diagnostic value is limited to *L. pneumophila* serogroup 1, but the promising fact for this screening test is that >80% of the infections are caused exactly by this strain. In addition to the safety of the patients, the results might have broader meaning since the screening test would comprise a quite large population [13]. The interpretation of the results of such a large group would presumably have implications on broadening the knowledge and fulfilling the gaps about the pathogenesis of the infection.

The first giant step in perceiving the true position of TNF-α inhibitors in increasing the susceptibility to *legionella* infection was taken by Directive concerning this issue, released on 7th of September 2011 by Food and Drug Administration in the USA. It said that the black box warning information for all of the TNF-α inhibitors had to be updated to include the increased risk for serious and sometimes fatal infection with *Listeria* and *Legionella*. This Directive was a result of 80 cases (of which 14 with fatal outcome) registered in the period between 1999 and 2012, who developed *Legionella* pneumonia after having received TNF-α inhibitors [44]. At the moment, relevant European institutions (European Working Group on Legionella Infection (EWGLI), European Centre for Disease Prevention and Control (ECDC)) do not have such an alert and their recommendations are a general advice for diagnosis and registration of legionellosis [6, 45], as well as surveillance in the countries included in the network of these institutions.

We are aware while TNF-α role in controlling infection against *L. pneumophilla* (as described above) provides pathophysiologic base supporting predisposition for legionellosis in patients treated with TNF-α inhibitor, it is not sufficient *per se* to establish direct causative relationship between these two entities. Nevertheless, the present review serves to highlight the possibility that TNF-α inhibitors, beside other reported opportunistic infections [22], might predispose the infection with *L.pneumophylla* too. Epidemiological support for this hypothesis arises from the largest case-series in the literature – the French registry of patients receiving TNF-α inhibitors [32], the FDA Directive [44], as well as from the fact that legionellosis was rarely reported in rheumatic patients not receiving TNF-α inhibitor [32].

Given the fact that this is a severe and potentially fatal but curable disease, maintaining a high index of clinical vigilance and systematic assessment of every symptom by the treating physician, is important to diagnose in time and adequately treat these patients (i.e. empiric administration of an antibiotic comprising *legionella*, until the aetiology of pneumonia is confirmed). A long-term follow-up might help to define better the clinical risk carried by anti-TNF-*α* agents in everyday clinical practice.

Previous review has several limitations. The exemption of non-English papers and relevant abstracts certainly has an impact on completing the picture of the topic discussed (e.g. additional cases from RATIO registry published in EULAR 2010 abstract book by Tubach et al. are not included in this review). The second issue relates to the imbalanced immune system in the population that is subject of this review, due to the primary chronic inflammatory disease. In addition, it is modulated by the conventional immunosuppressive therapy (cytostatics, glucocorticoids, non-biological DMARDs) and other co-morbid conditions, which altogether complicates the appropriate interpretation of the results from studies and clinical trials. Finally, previous studies have been performed mainly in patients with RA. However, this is not surprising having in mind that they comprise the majority of patients eligible to enter this type of studies: RA is the main indication for use of TNF-α inhibitor therapy [32] and an estimated 20% of RA patients receive such treatment [13].

In conclusion, to specify the characteristics of this relationship, it is necessary to define the actual size of the problem by diagnosing and reporting of legionellosis on regular basis. Also, additional target investigations and trials are needed to find the exact place of Legionnaires' disease in the mosaic of anti-TNF-α therapy. The future research on Legionnaires' disease in patients who are candidates for anti-TNF-α inhibitors therapy, should focus on several important issues: 1) Chemoprophylaxis [8]; 2) Investigations of intracellular cycle of *L. pneumophila* (potential development of screening test for detection of latent infection, analogue to Interferon-γ Release Assays in latent tuberculosis infection (LTBI) [39]); 3) Development of new TNF-α inhibitors. Differences have been reported in the risk of reactivation of LTBI when infliximab and etanercept have been used [16, 46] as well as differences in pharmacokinetics and modulation of TNF-α activity between the existing TNF-α inhibitors [47] The future of drugs directed against TNF-α lays in the creation of therapeutic agents adjusted to both endogenous kinetics of TNF-α and differences of TNF-α-biology in different diseases; 4) Vaccine. In vivo experiments on guinea-pigs showed that bacterial parts [48], secretory products

[49] and live avirulent vaccine [50] stimulated creation of cell-mediated protective immunity. Results from these animal models have not been verified and confirmed through clinical trials, and vaccine against Legionnaires' disease has not been developed yet [8]; 5) Engagement of public health system: continuing education and training of healthcare professionals who prescribe TNF-α inhibitors [13]; additional prevention strategies [29] and population-based studies to define the exclusion criteria in candidates for biological therapy [13]; precise registration of adverse effects; education of patients for early self-recognition of infection symptoms and signs and option for self-reporting the side effects of therapy; and 6) Infection control. Patients receiving TNF-α inhibitor therapy have to be advised to avoid exposure to aerosols from different water supply systems. Since the disease is not transmitted from human to human, the primary place in the infection control is given to surveillance of water supply systems (particularly in health care facilities), followed by use of efficacious disinfection agents [4, 6].

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