Recommendations for infectious disease screening in migrants to Western Europe with inflammatory arthropathies before starting biologic agents. Results from a multidisciplinary task force of four European societies (SIR, SER, SIMET, SEMTSI) facing the largest impact of the flow of migrants today

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Abstract

Objective

Inflammatory arthritis needs infectious disease screening before starting a biologic agent, however, few data are known about migrant patients, who represent a peculiar population which requires a multidisciplinary approach among international health specialists and should also be considered by health authorities. For this reason, the Italian and Spanish Societies of Rheumatology (SIR and SER) and Tropical Medicine (SIMET and SEMTSI) promoted a multidisciplinary task force in order to produce specific recommendations about screening and advices to be considered in migrant patients with inflammatory arthritis candidate to receive biological therapy, according to their geographical origin.

Methods

The experts provided a prioritised list of research questions and the eligible spectrum of inflammatory arthritis, biologic drugs and infectious disease were defined in order to perform a systematic literature review. A search was made in Medline, Embase and Cochrane library, updated to March 2015. Ubiquitous infections and HBV, HCV, HIV and tuberculosis that are already considered in national and international recommendations, were not included. The strength of each recommendation was determined.

Results

The task force members agreed on 7 overarching principles. The risk of reactivation of selected potentially latent infectious disease was addressed in migrants with inflammatory arthritis candidates for biologics was considered and 15 potentially relevant infections were identified.

Conclusion

Fifteen disease-specific recommendations were formulated on the basis of high level of agreement among the experts panel.

Key words

rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, anti-TNF, infections, systematic review

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Introduction

The use of biological agents has grown exponentially in rheumatology and other specialties. In rheumatic diseases, biological treatments have been largely used in inflammatory arthritides (IA) such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS), contributing to control disease progression and improving patients' quality of life. Their use has revealed an increased risk of serious adverse events, fostering new infectious events and, mostly, reactivation of chronic/latent infectious diseases (1). Granulomatous infections are widely documented in patients treated with biological agents, especially anti-TNF-α inhibitors, thus suggesting a class effect (2). For this reason, screening for active and latent chronic infectious diseases in patients who are candidates for biological agents is mandatory. In developed countries, screening for infectious diseases is generally limited to chronic viral hepatitis and latent tuberculosis infection (LTBI).

Increasing globalisation and the remarkable number of migrating and travelling people worldwide makes this approach no longer adequate. Migration between different epidemiological environments causes new challenges to health systems, which must be taken in account to ensure equitable access to care and an early identification of the various threats, risks and challenges of the migrant populations (3). In this framework, the new concept of global health is defined as 'health without borders', to interpret and examine the relationship between people and countries, based on globalisation and its impact on health. For this reason, new health-promotion programmes and screening strategies for the prevention and control of infectious diseases are needed today, particularly because the reactivation of neglected latent infections, due to underlying conditions, such as HIV infection, haematological malignancies, solid-organ transplantation or immunosuppressive therapies, may often result in severe and sometimes life-threatening manifestations and complications. Also, in the context of treatment with biological agents, reactivation of unusual infections, for which screening is not routinely provided, has been reported (4).

The correct management of patients coming from endemic areas for endemic, tropical and/or neglected disease who undergo biological treatment is a problem, which deserves consideration by rheumatologists. While in these cases a global work up of several diseases is not feasible, screening strategies and clinical monitoring can be personalised according to the region of origin.

In this regard, in accordance with the new concept of global health, a multidisciplinary approach among international health specialists is a fundamental but there is still the unmet need to approach problems in migrant patients that health authorities should consider. For this reason, the Italian and Spanish Societies of Rheumatology (SIR and SER) and Tropical Medicine (SIMET and SEMTSI) promoted a multidisciplinary task force in order to produce specific recommendations about screening and advices to be considered in migrant patients with IA candidate to receive biological therapy, according to their geographical origin. This aim was achieved following standard operating procedures, combining available evidence from medical literature with expert opinion (5). Our recommendations target all physicians and nurses who are involved in the care for patients with IA.

Materials and methods

Expert committee

The committee consisted of 11 rheumatologists, 10 tropical/infectious disease physicians, and 3 clinical epidemiologists, representing two European countries (Italy and Spain) that are currently facing the largest wave of migrants.

Definitions

In these recommendations, the term 'migrant' refers to people from countries/areas with negative net migration index (Central/South America, Asia, Africa, Eastern Europe), migrated to Western Europe (WE). WE was defined in accordance to United Nations Regional Groups definition. IA include RA, PsA, AS and undifferentiated arthritides.

Biologic drugs include anti-TNF-α (infliximab, etanercept, adalimumab, certolizumab pegol, golimumab), anti-CD20 (rituximab), anti-CTLA4 (abatacept), anti-IL6 (tocilizumab), anti-IL1 (anakinra).

Latent infections are defined as persistent infections that remain silent for a period of time and reactivate in the presence of immune disorders (opportunistic infections), despite being able to cause symptomatic infections also in immunocompetent hosts.

Development of recommendations

A preliminary search looked for evidence on the risk of infection between non-WE regions *versus* WE regions, with a special focus on countries with a negative migration index. For this purpose, official sources were preliminary searched, and when no sufficient evidence was retrievable, ad hoc searches of systematic reviews or primary studies were done. A world map of 20 geographical regions with relative prevalence of each infection was drawn using WE-prevalence as the denominator. These data enabled the expert panel to select the relevant infections to be included in the systematic searches.

The experts were invited to define the coverage of the recommendations including diseases, drugs, and infections, which were to be used as search terms for the systematic literature review.

At the end of the first task force meeting, 59 potentially relevant infections were identified and clinical questions were composed for the systematic literature reviews, according to a prespecified protocol.

Medline (via PubMed), Embase, Cochrane Central were searched until March 2015. As search terms, the MESH/Emtree terms for the defined IA, biologic drugs and selected infections were combined (Appendices). Only articles in English and concerning patients aged >16 years were included. Other papers that were considered relevant in the opinion of the experts could be added. The results of the systematic literature review (performed in duplicate by CAS, GS, MM, DB, JSC, MAA, ARM, CFE) were sent to the committee before the second meeting, together with proposals for recommendations.

After examining the results of the literature search, the expert panel defined a list of potential interesting pathogens to be included in the recommendations. HBV, HCV, HIV and TB (except for multi-drug resistant TB due to the complexity of its management), already taken into account in several national and international recommendations, were excluded.

The recommendations summarised in this article represent a consensus of published evidence and expert opinions. For each recommendation we used a widely-accepted hierarchy for categorising the available evidence and the strength of the recommendations (evidence categories A–D) (Table I). Overarching principles and specific recommendations were separately voted and scored from 0 (no agreement with) to 10 (maximal agreement). The

Table I. Evidence categories and strength of recommendations.

Category	Evidence
Ia	Meta-analysis of randomised controlled trials
Ib	Randomised controlled trial
II	Prospective controlled intervention study without randomisation
III	Descriptive/analytic study (including case-control, cross-sectional, case series)
IV	Expert committee reports or opinion or clinical experience of respected authorities or both
Strength	**Based on**
A	Category I evidence
B	Category II evidence or extrapolated recommendations from category I evidence
C	Category III evidence or extrapolated recommendations from category I or II evidence
D	Category IV evidence or extrapolated recommendations from category II or III evidence

Table II. List of latent infection considered by the panel of expert for recommendation.

Disease	Screening	Candidates for screening	Available tests
Mycobacterial diseases			
Hansen's diseases	No		None
Non-TB mycobacteria	No		None
MDR-TB	Yes	All patients[§]	TST/IGRAs
Bacterials diseases			
Brucellosis	No		Serology
Salmonellosis (typhi/paratyphi)	Yes	Patients from highly endemic areas with cholelithiasis/urinary tract defect	Stool and urine cultures
Parasitic diseases			
Leishmaniasis	No		Serology, PCR
Babesiosis	No		Blood smears, serology, PCR
Strongyloidiasis	Yes	Migrants from endemic areas and autochthonous patients with eosinophilia	Serology and stool test if available
Cysticercosis	No		Serology
Chagas disease	Yes	Patients from/whose mother was born in/blood transfused in endemic area	Serology
Viral diseases			
HEV	No		Serology, PCR
HTLV-1	No		Serology, PCR
Fungal diseases			
Histoplasmosis	Yes	Patients from endemic areas with suggestive history/radiological signs	Serology
Coccidioidomycosis	Yes	Patients from endemic areas and compatible clinical symptoms/history	Serology
Paracoccidioidomycosis	No		Serology

n.a.: not applicable; TB: tuberculosis; MDR-TB: Multi drug resistant-TB; TST: Tuberculin skin test; IGRA: Interferon gamma release assay.
[§]: not specific screening for MDR-TB; same screening applied for Latent Tuberculosis Infection.

means and standard deviation (SD) of the scores were calculated to determine the level of agreement among the experts panel for each recommendation.

Results

Fifteen potentially relevant infections were identified (Table II).

The task force members agreed on 7 overarching principles and 15 disease-specific recommendations, reaching a high level of agreement among the experts panel (Table III).

For every considered pathogen we present briefly the disease, along with the available evidence of reactivation in immunocompromised patients, with particular reference to IA patients ongoing biological treatment. Epidemiological data are summarised in Table IV.

Statements

Each recommendation is followed in brackets by the grade of the evidence and the strength of the recommendation.

Overarching principles

The Committee considered that some aspects related to the screening of migrant people and treatment of IA might form a framework on which specific recommendations could be based. These items were therefore considered to constitute overarching principles, although they were discussed and voted on.

A. Migrants (included those who are considered by authorities illegal immigrants that do not have work permits and residence) should be submitted to the standard check-up and screening applied to all candidates for biologics.
B. Before starting biologics, the individual risk of infectious diseases should be estimated on the basis of the epidemiological risk linked to the country of origin of the patient
C. When a specific infectious disease risk is identified, an appropriate screening should be performed, if available.
D. If a latent infection is suspected or diagnosed, the patient should be referred to a tropical/infectious diseases specialist to exclude active disease and to consider the availability of effective eradication or prophylactic treatments before starting biologic therapy.
E. When appropriate screening for latent infections is not available, tropical/infectious disease specialist advice should be sought to evaluate the risk-benefit ratio of starting immunomodulatory treatment and to set up suitable clinical monitoring.
F. In migrant patients with IA, vaccination should be performed according to the national recommendations of the country where the patient should be treated. Vaccination should be completed before starting biological treatment.
G. In patients with IA who have already started a biologic treatmen the risk of infection reactivation should be considered by a tropical/infectious disease specialist according to the country-specific potential exposure.

Disease-specific recommendations

• Hansen's disease

Mycobacterium leprae causes a chronic granulomatous disease with highly variable clinical presentations, ranging from skin lesions to severe damage to nerves and other organs, including bones and joints. The disease is still endemic in all countries of the African and South-East Asia regions and in most countries of the Americas, Western Pacific and Eastern Mediterranean Region (6).

In IA patients on biologics, several cases of leprosy have been reported, often with a relatively shorter time of progression. Infliximab has been associated with 2 cases of leprosy (7, 8), both the cases were reported in South America. Both treatments were stopped and proper antimicrobial therapy was started with resolution of the infection. Moreover, two cases have been reported in patients treated with etanercept (9, 10), one with adalimumab (11), and one with tocilizumab (12). One patient treated with etanercept was previously treated with infliximab. In one case, leprosy was defined as paucibacillary (less than 5 lesions), biologic treatment was stopped and then restarted after 3 months of antileprosy treatment. One patient that developed leprosy was from Greece.

Recommendation 1

Hansen's disease (leprosy) should be ruled out in patients coming from high prevalence countries and presenting unexplained cutaneous lesions or signs of peripheral neuropathy; biopsies of any suspicious skin lesion should be performed before starting biological treatment. (grade of evidence III; strength of recommendation D; agreement (SD) 9.69 (0.48))

Non-tuberculous mycobacteria (NTM)

NTM include about 100 different species of mycobacteria omnipresent in the environment. The geographical distribution of NTM species differs strongly worldwide and it may determine, in part, a different burden and outcome of NTM disease in each region (13).

NTM might cause opportunistic diseases in condition of immunosuppression and they are an increasingly recognised problem in the setting of IA patients on biologics and in particular on anti-TNF. Multiple species, both with high (*M. marinum, M. xenopi, M. szulgai, M. kansasii, M. mucogenicum*) and low (*M. fortuitum, M. peregrinum, M. haemophilum, M. chelonae*) pathogenicity have been reported in patients on biologic therapy, both with anti-TNF and tocilizumab (14-44). Recently, NTM pulmonary infections in patients with RA treated with biologic agents in Japan showed that *M. avium* complex was the most frequent, followed by *M. gordonae*. Clinical manifestations of the infection vary widely, besides pulmonary manifestations, also skin and soft tissue infection, infectious tenosynovitis, septic arthritis, lymphadenitis, psoas muscle abscesses, spondylodiscitis, endophthalmitis and hepatitis have been reported. Infections have been fatal in some cases. Nationality was available for few studies, and patients were from South Central USA, Netherlands, South Korea and Japan. A recent study reported an incidence of NTM infection in RA treated with anti-TNF of 0.4 x 1000 person years, while another study based in USA identified 211 cases of NTM, that were more likely to live in urban settings, have pul-

Table III. Overarching principles and disease-specific recommendations: level of agreement among the experts panel.

Overarching principles	
A.	Migrants (included those who are considered by authorities illegal immigrants that do not have work permits and residence) should be submitted to the standard check-up and screening applied to all candidates for biologics.
B.	Before starting biologics, the individual risk of infectious diseases should be estimated on the basis of the epidemiological risk linked to the country of origin of the patient.
C.	When a specific infectious disease risk is identified, an appropriate screening should be performed, if available.
D.	If a latent infection is suspected or diagnosed, the patient should be referred to a tropical/infectious diseases specialist to exclude active disease and to consider the availability of effective eradication or prophylactic treatments before starting biologic therapy.
E.	When an appropriate screening for latent infections is not available, a tropical/infectious diseases specialist advice should be sought to evaluate the risk-benefit ratio of starting an immunomodulatory treatment and to set up a suitable clinical monitoring.
F.	In migrant patients with IA, vaccination should be performed according to the national recommendations of the country where the patient should be treated. Vaccination should be completed before starting biological treatment.
G.	In patients with IA, who have already started a biologic treatment, the risk of infection reactivation should be considered by a tropical/infectious diseases specialist according to the country specific potential exposure

Disease specific recommendations	Agreement (SD)
Recommendation 1. Hansen's disease (leprosy) should be ruled out in patients coming from high prevalence countries and presenting unexplained cutaneous lesions or signs of peripheral neuropathy; biopsies of any suspicious skin lesion should be performed before starting biological treatment.	9.69 (0.48))
Recommendation 2. NTM disease should be ruled out in patients with respiratory symptoms, evidence of bronchiectasis or other architectural lung abnormalities, regardless the country of origin. In these patients, smear and culture of three sputum specimens and/or bronchoalveolar lavage may be used to rule out NTM.	9.31 (1.14)
Recommendation 3. Candidates to receive biological treatment coming from high prevalence countries for MDR-TB, and with positive LTBI screening, should be referred to a tropical/infectious specialist.	9.06 (0.93)
Recommendation 4. Screening for brucellosis in asymptomatic patients is not recommended. Brucellosis should be ruled out in febrile patients coming from high prevalence countries and exposed to environmental risk factors (consumption of unpasteurised animal milk or direct contact with potentially infected animals). In these patients, serological and cultural tests should be performed before starting biological treatment. (grade of evidence II; strength of recommendation C; agreement (SD))	9.31 (1.01)
Recommendation 5. *Salmonella* spp. carrier status should be considered in patients coming from high prevalence countries, with cholelithiasis or defect in the urinary tract, in particular if previous episodes of fever and diarrhea are reported. However, stool or urine culture should be performed only on a case by case evaluation, before starting biological treatment.	8.56 (1.36)
Recommendation 6. Screening for Leishmaniasis in asymptomatic patients is not recommended. Leishmaniasis should be ruled out in patients with fever, and/or hepatosplenomegaly and pancytopenia coming from endemic countries, before starting biological treatment.	9.69 (0.60)
Recommendation 7. Babesiosis screening of asymptomatic patients coming from endemic countries is not recommended before starting biological treatment.	9.69 (0.60)
Recommendation 8. Strongyloidiasis should be considered in all migrants from endemic areas and autochthonous patients with eosinophilia. In these patients, a serologic test, and when available a stool-based test, should be performed before starting biological treatment.	9.63 (0.72)
Recommendation 9. Routinely screening of cysticercosis in asymptomatic patients before starting biological treatment is not recommended. Neurocysticercosis should be ruled out in patients with epilepsy coming from endemic countries.	9.69 (0.60))
Recommendation 10. Chagas disease should be considered in patients living or long-staying (>3 mo) in endemic areas, in patients whose mother was born in a Chagas disease endemic area and in patients who received a blood transfusion in endemic areas. In these patients serological testing should be performed before starting biological treatment.	9.81 (0.40)
Recommendation 11. Chronic hepatitis E should be considered in patients with not otherwise explained liver enzymes abnormalities coming from countries with high prevalence. In these patients, serology should be performed before starting biological treatment.	9.44 (0.63)
Recommendation 12. HTLV-1 screening of asymptomatic patients coming from endemic countries is not recommended before starting biological treatment.	9.56 (0.81)
Recommendation 13. Histoplasmosis should be considered in patients coming from endemic areas. In these patients, a careful clinical history and chest radiography should be performed before starting biological treatment. In presence of suggestive history or radiological signs, serological and urinary antigen testing should be performed.	9.50 (0.52)
Recommendation 14. Coccidioidomycosis should be considered in patients from endemic areas with a history of pneumonia, associated to fatigue, arthralgias, and/or erythema nodosum. In these patients, serology should be performed before starting biological treatment.	9.19 (0.91)
Recommendation 15. Paraccoccidioidomycosis should be ruled out in patients with not otherwise explained lung disease coming from areas with high prevalence. Screening of asymptomatic patients is not recommended before starting biological treatment.	9.56 (0.63)

Table IV. Disease-specific epidemiology: highly endemic areas of each pathogen.

Macroarea	Hansen's disease	Non tuberculous mycobacteria	Multidrug resistant tuberculosis	Brucellosis	Salmonellosis	Leishmaniasis	Babesiosis	Strongyloidiasis	Cysticercosis	Chagas disease	HEV	HTLV-1	Histoplasmosis	Coccidioidomycosis	Paraccocidioidomycosis
Australia and New Zealand (Australia, New Zealand)															
Caribbean (Cuba, Dominican Republic, Haiti, Jamaica, Puerto Rico, The Bahamas, Trinidad and Tobago)					X							X			
Central America and Mexico (Belize, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama)				X	X			X	X	X	X		X	X	X
Central Asia (Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan)			X	X	X						X				
Eastern Africa (Burundi, Djibouti, Eritrea, Ethiopia, Kenya, Madagascar, Malawi, Mozambique, Rwanda, Somalia, Somaliland, South Sudan, Uganda, United Republic of Tanzania, Zambia, Zimbabwe)	X		X	X	X	X		X	X		X	X			
Eastern Asia (China, Japan, Mongolia, North Korea, South Korea, Taiwan)			X		X			X	X		X	X			
Eastern Europe (Belarus, Bulgaria, Czech Republic, Hungary, Moldova, Poland, Romania, Russia, Slovakia, Ukraine)			X												
Melanesia (Fiji, New Caledonia, Papua New Guinea, Solomon Islands, Vanuatu)	X				X										
Central Africa (Angola, Cameroon, Central African Republic, Chad, Democratic Republic of the Congo, Equatorial Guinea, Gabon, Republic of Congo)	X		X		X			X	X		X	X			
Northern Africa (Algeria, Egypt, Libya, Morocco, Sudan, Tunisia, Western Sahara)	X			X	X						X				
Northern America (Canada, Greenland, USA)							X	X					X	X	
Northern Europe (Denmark, Estonia, Finland, Iceland, Ireland, Latvia, Lithuania, Norway, Sweden, United Kingdom)			X												
Southern America (Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Falkland Islands, Guyana, Paraguay, Peru, Suriname, Uruguay, Venezuela)	X			X	X	X		X	X	X		X	X	X	X
South-Eastern Asia (Brunei, Cambodia, East Timor, Indonesia, Laos, Malaysia, Myanmar, Philippines, Thailand, Vietnam)	X		X	X	X			X	X		X				
Southern Africa (Botswana, Lesotho, Namibia, South Africa, Swaziland)	X		X		X				X		X				
Southern Asia (Afghanistan, Bangladesh, Bhutan, India, Iran, Nepal, Pakistan, Sri Lanka)	X		X	X	X	X			X		X				
Southern Europe (Albania, Bosnia and Herzegovina, Croatia, Greece, Kosovo, Macedonia, Montenegro, Portugal, Republic of Serbia, Slovenia)				X											
Western Africa (Benin, Burkina Faso, Gambia, Ghana, Guinea, Guinea Bissau, Ivory Coast, Liberia, Mali, Mauritania, Niger, Nigeria, Senegal)	X		X		X				X		X	X			
Western Asia (Armenia, Azerbaijan, Cyprus, Georgia, Iraq, Israel, Jordan, Kuwait, Lebanon, Northern Cyprus, Oman, Palestine, Qatar, Saudi Arabia, Syria, Turkey, United Arab Emirates, Yemen)			X	X	X						X				
Western Europe (Austria, Belgium, France, Germany, Luxembourg, Netherlands, Switzerland)							X								

monary extra-articular RA, overall comorbidities, asthma, COPD and GORD than controls.

Recommendation 2

NTM disease should be ruled out in patients with respiratory symptoms, evidence of bronchiectasis or other architectural lung abnormalities, regardless the country of origin. In these patients, smear and culture of three sputum specimens and/or bronchoalveolar lavage may be used to rule out NTM. (grade of evidence III; strength of recommendation D; agreement (SD) 9.31 (1.14))

Multidrug resistant tuberculosis (MDR-TB)

MDR-TB is defined as a form of TB resistant at least to isoniazid and rifampicin, which requires longer, expensive and more toxic treatment regimens (45). MDR-TB cases have been reported in almost all countries, but the

incidence in low resource countries is much higher and further increasing. No differences with latent TB have been reported in patients with IA treated with biologic. We suggest that patients coming from a high burden MDR-TB area, diagnosed with LTBI in the context of a screening, other than MDR-TB contact tracing, should receive LTBI treatment. This is suggested because, even in those areas, the latent infections can be sustained by a susceptible strain of *M. tuberculosis*.

Recommendation 3

Candidates to receive biological treatment coming from high prevalence countries for MDR-TB, and with positive LTBI screening, should be referred to a tropical/infectious disease specialist. (grade of evidence IV; strength of recommendation D; agreement (SD) 9.06 (0.93)).

Brucellosis

Brucellosis is one of the most common and important zoonotic diseases worldwide. It is transmitted through the consumption of infected, unpasteurised animal milk or direct contact with infected wild and domestic animals. The human pathogens (*Brucella abortus*, *B. suis*, *B. canis* and *B. melitensis*) can cause systemic infections. The disease is widespread in European Mediterranean countries, north and east Africa, Middle East, south and central Asia and Central and South America. Only few cases of brucellosis have been reported in association with anti-TNF-α treatment, two cases have been reported in association with infliximab (46, 47). One infection was linked to consumption of unpasteurised milk products. Treatment was discontinued and antimicrobial therapy was started with resolution of the disease.

At the time, there is no evidence supporting a screening of patients who are to be treated with biologics, while brucellosis should be considered in case of compatible symptoms/history, especially if the patient comes from countries with high prevalence. Finally, the patients should be advised in order to avoid the consumption of unpasteurised milk and cheese.

Recommendation 4

Screening for brucellosis in asymptomatic patients is not recommended. Brucellosis should be ruled out in febrile patients coming from high prevalence countries and exposed to environmental risk factors (consumption of unpasteurised animal milk or direct contact with potentially infected animals). In these patients, serological and cultural tests should be performed before starting biological treatment. (grade of evidence II; strength of recommendation C; agreement (SD) 9.31 (1.01))

Salmonellosis

Typhoid fever is a severe systemic infection caused by the bacterium *Salmonella enterica* serotype typhi, characterized by fever with or without accompanying symptoms (48). Other *Salmonella* serotypes, particularly *S. enterica* serotype paratyphi A, B, or C, can cause a similar syndrome. Today, most of the burden of the disease occurs in countries where sanitary conditions remain poor, with a high incidence in South-central and South-east Asia. The rest of Asia, Africa, Latin America, the Caribbean, and Oceania, except for Australia and New Zealand, have a medium incidence (49). Several cases of typhoid fever or other diseases caused by *Salmonella* spp. have been reported in IA patients treated with biologics, especially with anti-TNF. Most infections were caused by *S. enterica*, in 14 cases. Few cases have been reported for other serotypes, as paratyphi in one case treated with infliximab, 1 case in *S. dublin* and *S. enterica haddar*. Few cases of septic arthritis caused by Salmonella have been reported, one in association with etanercept. Based on the Spanish register BIOBADASER, 17 cases of non-typhi Salmonella infections in patients with IA on anti-TNF therapy were reported, of which 9 presented a severe systemic infection, accounting for an incidence of 0.73/1000 PYs, with a relative risk (RR) of 2.07 (95% CI: 0.27–15.73), compared to IA patients not receiving anti-TNF (14, 22, 31, 50-61).

General advice on measures to prevent faecal-oral transmitted diseases and to avoid high-risk food reduces the risk of *Salmonella* infections in RA patients receiving anti-TNF (62).

Recommendation 5

Salmonella spp. carrier status should be considered in patients coming from high prevalence countries, with cholelithiasis or defect in the urinary tract, in particular if previous episodes of fever and diarrhoea are reported. However, stool or urine culture should be performed only on a case by case evaluation, before starting biological treatment. (grade of evidence III; strength of recommendation D; agreement (SD) 8.56 (1.36))

Leishmaniasis

Leishmaniasis is a protozoal zoonosis caused by *Leishmania spp*, transmitted to humans by sand flies. The clinical spectrum includes cutaneous, mucocutaneous, and visceral (VL) forms. The latter, classically characterised by fever, hepatosplenomegaly and pancytopenia, is fatal in 85-90% of cases if not treated (63). The leishmaniases are widely dispersed, but most of the disease burden is concentrated in a few regions: close to 90% of VL cases occur in the Indian subcontinent, East Africa, with the highest incidence in Ethiopia and Sudan, and Brazil. Other foci are the Mediterranean Basin, the Middle East and Central Asia, China and the rest of South America. Several cases of visceral leishmaniasis have also been reported in association with biologics (11, 64-80), most of which were in Spain, one was also reported in Brazil, Portugal and France, however the patient was Algerian. Both visceral and cutaneous cases of leishmaniasis have been reported in patients undergoing anti-TNF monoclonal antibodies, but a relative-risk has not been definitely established. Currently, there is no evidence supporting the screening in patients candidates to immunosuppressants (81).

Recommendation 6

Screening for Leishmaniasis in asymptomatic patients is not recommended. Leishmaniasis should be ruled out in patients with fever, and/or hepatosplenomegaly and pancytopenia coming from endemic countries, before starting biological treatment. (grade of evidence III; strength of recommendation D; agreement (SD) 9.69 (0.60))

Babesiosis

Tick-transmitted hemoparasites of the protozoan genus *Babesia* are the second most common blood-borne parasites of mammals after trypanosomes. Humans are commonly infected by the bite of an infected *Ixodes* tick. *B. microti* and *B. divergens* are the two strains responsible for human disease in the United States and Europe, respectively (82-85). Occasionally, human babesiosis has been reported from Australia, Taiwan, Japan and Korea (85, 86).

Currently, there are no reports of babesiosis in patients on biologics, and we consider that, at the moment, a screening is not recommended. On the other hand, babesiosis should be considered in the differential diagnosis of febrile illnesses in patients who report a tick bite from an endemic area.

Recommendation 7

Babesiosis screening of asymptomatic patients coming from endemic countries is not recommended before starting biological treatment. (grade of evidence III; strength of recommendation D; agreement (SD) 9.69 (0.60))

Strongyloidiasis

Strongyloides stercoralis is a nematode which infects humans by direct penetration of skin in contact with contaminated soil. Walking barefoot is the main risk factor for the acquisition of the infection, in areas with poor sanitary standards. It is endemic in tropical and subtropical areas of the world including Southeast Asia, Latin America, sub-Saharian Africa, and parts of the southeastern US, but also in some temperate areas with low endemicity (87). So far, only one case of severe strongyloidiasis has been reported in a Filipino patient treated with adalimumab fo rRA (88).

All migrants from endemic areas and autochthonous patients with eosinophilia should be screened before starting any immunosuppressant therapy.

Recommendation 8

Strongyloidiasis should be considered in all migrants from endemic areas and autochthonous patients with eosinophilia. In these patients, a serologic test, and when available a stool-based test, should be performed before starting biological treatment. (grade of evidence III; strength of recommendation D; agreement (SD) 9.63 (0.72))

Cysticercosis

Taenia solium is a cestode widely diffused in areas of poor hygienic conditions, characterised by improper disposal of human and pig feces (89). *T. solium* infection is endemic in less developed countries, in highlands or tropical areas, in Central and South America, and non-Muslim populations of South and South-East Asia and sub-Saharan Africa. The accidental ingestion of its eggs can cause cysticercosis (CC), characterised by tissue invasion by the metacestode larval stage, occurring more frequently in the central nervous system (neurocysticercosis, NCC) (90). The symptoms are related to the localisation of the cysts, their number and to the response of the host's immune system (89). It is estimated that NCC causes about 30% of cases of epilepsy in endemic, low resources countries (90).

No cases of cysticercosis have been reported in association with biologic treatment. Currently, the screening it is not recommended in asymptomatic patients. Epilepsy in adults coming from endemic countries should be carefully evaluated with a combination of criteria, including imaging data and serological tests (89).

Recommendation 9

Routinely screening of cysticercosis in asymptomatic patients before starting biological treatment is not recommended. Neurocysticercosis should be ruled out in patients with epilepsy coming from endemic countries. (grade of evidence IV; strength of recommendation D; agreement (SD) 9.69 (0.60))

Chagas disease

Chagas disease, also known as American trypanosomiasis, is a neglected parasitic infection caused by *Trypanosoma cruzi*, endemic in South, Central and part of North America (Mexico and possibly South Texas). Although the vector is not present in Europe, the disease has recently emerged in most European countries, due to increasing immigration from Latin America in the last decade (91).

There are only two reported cases of RA and Chagas disease and neither of the patients was on biologic therapy (92, 93). Although the role of biologic drugs on Chagas disease progression is still unknown, screening for Chagas disease should be performed in all patients living or long-staying (>3 mo) in an endemic area, in patients whose mother was born in a Chagas disease endemic area and in patients who received a blood transfusion in endemic areas.

Recommendation 10

Chagas disease should be considered in patients living or long-staying (>3 mo) in endemic areas, in patients whose mother was born in a Chagas disease endemic area and in patients who received a blood transfusion in endemic areas. In these patients serological testing should be performed before starting biological treatment. (grade of evidence III; strength of recommendation D; agreement (SD) 9.81 (0.40))

HEV

Hepatitis E is an enterically-transmitted, acute viral hepatitis. Hepatitis E virus (HEV) is a RNA virus spread by faecal contaminated water and consumption of animal products in endemic areas. Person-to-person transmission is uncommon. Nosocomial and vertical transmission, as well as via blood transfusion, have also been described (94). The highest incidence of HEV infection is in Asia, Africa, Middle East and Central America. Most cases in western countries occur in travellers returning from endemic areas, but sporadic cases not associated with travel have been reported, too (95).

A recent retrospective study reported 23 cases of HEV reactivation or infection in IA patients treated with biologics, mainly anti-TNF but also rituximab, abatacept and tocilizumab (96-98). One case was also reported in the Orencia and Rheumatoid Arhtritis (ORA) registry, the patient had been previously treated with leflunomide and 3 different anti-TNF (etanercept, adalimumab and infliximab) and was concomitantly treated with methotrexate 15 mg/week

(99). Few infections were linked to recent travels to Spain and consumption of contaminated chorizo, while one case with uncooked shellfish.
The screening for HEV is not recommended routinely, but the use of diagnostic test (serologic and molecular test) before and during treatment with biologics should be considered in migrants with unexplained liver enzymes abnormalities. Finally, travellers to endemic areas should be advised to prevent faecal-orally transmitted infections, such as avoiding drinking water of unknown purity, uncooked shellfish, and uncooked fruits or vegetables.

Recommendation 11
Chronic hepatitis E should be considered in patients with not otherwise explained liver enzymes abnormalities coming from countries with high prevalence. In these patients, serology should be performed before starting biological treatment. (grade of evidence III; strength of recommendation D; agreement (SD) 9.44 (0.63))

Human T-lymphotropic virus (HTLV-I)
This is a RNA human retrovirus, estimated to infect 10 to 20 million people worldwide, but is associated with disease in less than 5% of infected individuals. HTLV-1 is transmitted by breast feeding, although transmission also can occur via blood transfusion, sexual intercourse or sharing of needles. In some areas in Japan, sub-Saharan Africa, the Caribbean and South America more than 1% of the general population is infected (100, 101). The virus is associated with three categories of severe disease: hematologic malignancy (adult T-cell leukaemia/lymphoma) (ATL), inflammatory syndromes (HTLV-1-associated myelopathy/tropical spastic paraparesis, arthropathy and uveitis among others), and opportunistic infections (including *Strongyloides stercoralis* hyperinfection and others) (101-103). HTLV-1-associated arthropathy resembles RA, with synovial proliferation and a positive rheumatoid factor (104).
Ten HTLV-1–positive patients with RA have been treated with anti-TNF, and during 2 years of observation none developed ATL. However, HTLV-1–positive patients with RA had higher inflammation and greater resistance to anti-TNF treatment than HTLV-1–negative patients (105).
At the moment, there is no evidence supporting the indication of HTLV-1 screening in IA patients from endemic areas, candidates to biological treatment.

Recommendation 12
HTLV-1 screening of asymptomatic patients coming from endemic countries is not recommended before starting biological treatment. (grade of evidence III; strength of recommendation D; agreement (SD) 9.56 (0.81))

Histoplasmosis
Histoplasma capsulatum is a dimorphic fungus responsible for the most common endemic mycosis causing human infection. The endemic area includes the Ohio and Mississippi River valleys, Central and South America, and microfoci in the Eastern United States, southern Europe, Africa, and Southeastern Asia (106). In immunocompetent individuals, the infection is usually a self-limited febrile illness although occasionally it evolves toward a chronic pulmonary infection. Conversely, immunosuppression and immunosuppressants, including biologic and other immunomodulatory therapies for rheumatic diseases, are a well-known risk factor for life-threatening disseminated forms, extrapulmonary disease or reactivation of latent infections (107, 108). Histoplasmosis might be the most common invasive fungal infection reported in patient receving biologic agents, and several cases of histoplasmosis have been widely reported (14, 31, 59, 107, 109-127). Nine cases of histoplasmosis have been reported in the SABER (Safety Assessment of Biologic Therapy) Study, conducted in the USA (14). Most patients developed pulmonary histoplasmosis, but progressive dissemination, and also panniculitis and focal myositis have been described. Fatal cases may also occur.
Since most of the available clinical information on histoplasmosis in patients receiving anti-TNF agents is based on case reports and small case series, the recommendations regarding diagnosis and management are based on expert opinion (128, 129). However, in patients coming from endemic areas, a screening for a clinical history of histoplasmosis and a chest radiography should be considered. In presence of a history of pulmonary infection, and/or of radiographic findings showing infiltrates, nodules, or lymphadenopathy without a clear etiology, serology for *Histoplasma* should be performed.

Recommendation 13
Histoplasmosis should be considered in patients coming from endemic areas. In these patients, a careful clinical history and chest radiography should be performed before starting biological treatment. In presence of suggestive history or radiological signs, serological and urinary antigen testing should be performed. (grade of evidence III; strength of recommendation D; agreement (SD) 9.50 (0.52))

Coccidioidomycosis
Coccidioidomycosis is caused by inhalation of spores (arthroconidia) of dimorphic fungi of the genus *Coccidioides*. These are endemic in some deserts in the United States (Arizona, California, New Mexico and Texas), in parts of Mexico and Central and South America (130).
Several cases of coccidioidomycosis have been reported in IA patients receiving biologics (14, 20, 31, 131-136). The infections were localised, mainly pneumonia, or disseminated, while few cases were asymptomatic and diagnosed after testing. Most of the patients were from Arizona, Texas, New Mexico.
Based on these observations, in patients coming from US States of Arizona, California, New Mexico and Texas or from endemic areas of Mexico, Central and South America, an accurate clinical history should be taken to detect a possible, previous symptomatic coccidioidomycosis and coccidioidal serology prior to biological therapy should be considered. Specific serologic tests (immunodiffusion, tube precipitin-reacting antigen, complement fixation, enzyme-linked immuno-

assay) for both IgM and IgG antibodies are available. Direct smear examination and sputum culture can be useful in course of pneumonia.

Recommendation 14

Coccidioidomycosis should be considered in patients from endemic areas with a history of pneumonia, associated to fatigue, arthralgias, and/or erythema nodosum. In these patients, serology should be performed before starting biological treatment. (grade of evidence III; strength of recommendation D; agreement (SD) 9.19 (0.91))

Paraccoccidioidomycosis

Paracoccidioidomycosis is an inflammatory granulomatous systemic disease endemic in Latin America from Mexico to Argentina due to a dimorphic fungus, *Paracoccidioides brasiliensis* (137). In recent years, a rise in imported paracoccidioidomycosis has been observed in Europe, due to the increase of international travels and migrant flows (138).

So far, one case of paracoccidioidomycosis associated with biologic therapies has been reported in patient living in Brazil (139).

Currently we consider that an active screening of the disease is not recommended.

Recommendation 15

Paraccoccidioidomycosis should be ruled out in patients with not otherwise explained lung disease coming from areas with high prevalence. Screening of asymptomatic patients is not recommended before starting biological treatment. (grade of evidence III; strength of recommendation D; agreement (SD) 9.56 (0.63))

Discussion

These recommendations for infectious disease screening in migrant patients with IA starting biologic drugs are based on the current evidence resulting from the systematic literature review and the opinion of selected experts in the fields of rheumatology and tropical/infectious diseases from Italy and Spain. These two countries have experienced a significant flow of migrants in the last decade and are currently facing a new wave that has raised the concern at EU and international level. Unfortunately, high-grade evidence on the risk of reactivation of latent infections in this population, and on the utility of screening and prophylaxis strategies is not available. The highest grade of strength of a recommendation is therefore C. The literature on diagnostic accuracy of screening tests as well as on the efficacy of prophylaxis in the general population without IA were not systematically reviewed, and the experts formulated recommendations based on their knowledge and experience. A preliminary search on the migratory flows and country-specific relative risks of latent, hidden or opportunistic infection was performed, although not systematically, in order to define the potential burden of such infections. Our literature search focused essentially on three important aspects of migration-related infectious risk: the incidence of latent and opportunistic infections in IA on biologics, the potentially advantage of a screening and the efficacy and safety of prophylaxis measures.

We should acknowledge that the grading of the available evidence can differ between the three aforementioned aspects: higher level evidence is available for the incidence of infections in IA patients on biologics, but with little information (even absent) on the origin of patients, and most studies are underpowered with regard to rare exposure. Not even the new registers that have been established in developing countries (South Africa, Brazil) have yet provided information about the risk of infection in settings with high exposure to infectious agents relevant to migrant populations. In particular, helminths and protozoa that are parasites of the gastrointestinal tract are most prevalent in tropical regions. For this reason, patients and travellers derived from these areas with a diagnosis of a rheumatic disease may be at high risk for a significant re-exacerbation of the intestinal disease. Therefore, the rheumatologist should always be very vigilant when migrants or travellers affected with rheumatic diseases derive from these continents. In fact, the Brazilian Society of Rheumatology has already published recommendations for the diagnosis and management of intestinal parasitic infections in patients with rheumatic diseases, (RA, systemic lupus erythematosus and spondyloarthritis) (140).

Moreover, it is important to stress the fact that migrants and travellers, affected by rheumatic diseases, may have travelled in several countries before getting to the European soil. Therefore, the rheumatologist should always obtain detailed information on the countries visited to create the map of the risk and orientate the investigation for an occult infectious/parasitic diseases,

.For preventive measures, no sufficient data were available to draw conclusions in the specific sub-population of migrant people. Therefore, for these recommendations the experts have taken into account their knowledge of and experience on the general population.

Regarding the vaccination policies to be applied to IA population, considering the indication, the efficacy and the safety of each vaccination, the panel agreed on considering the need of a specific document to address this complex issue. At the moment, the panel agreed that in migrant IA patients vaccinations should be performed according to the national recommendations of the country where the patient is treated with biologic agents.

The results of agreement voting are therefore of particular importance since they represent the overall interpretation by the panel of experts of the evidence on all aforementioned aspects of infectious risk in migrant patients with IA starting biologics, in particular looking at the new biological drugs available in 2016 (141).

The recommendations will need to be updated on a regular basis, since epidemiological changes will occur over the time and new evidence hopefully will become available with regard to current and new biologic drugs and emerging infectious risks.

Other infections might be added to this list in the future, considering that the possible increase of immunosuppressant therapies in low-income countries might permit to identify other agents with the same characteristics.

Key messages

- Few data are available on the risk of latent infections reactivation in migrants
- The individual risk of infectious diseases should be estimated on the basis of epidemiological risk in the country of origin
- When an infectious disease is suspected, appropriate screening should be performed
- Tropical/infectious disease specialist advice should be sought when screening for latent infections is not available

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