Review

Rheumatological patients undergoing immunosuppressive treatments and parasitic diseases: a review of the literature of clinical cases and perspectives to screen and follow-up active and latent chronic infections

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Received on October 14, 2013; accepted in revised form on February 18, 2014.

Clin Exp Rheumatol 2014; 32: 587-596.

Key words: rheumatic diseases, immunosuppressive therapies, parasitic infections, parasitic screening flow-chart

Competing interests: none declared.

ABSTRACT

Objective. *Nowadays, several potent immunosuppressive drugs are available for patients with rheumatologic disorders. In general, these treatments are acceptably well tolerated. Nevertheless, in patients with rheumatic diseases, who are taking immunosuppressive drugs, an increased risk of bacterial, viral and fungal, as well as parasitic infections, exists.*

Methods. *We have reviewed literature, on PubMed library, on the topic "parasitic infections in rheumatic disease patients treated with immunosuppressive drugs, including biological therapies". We used no language or time restrictions. Search was concluded on January 15th 2014. We grouped all parasitic events among rheumatologic, therapeutically immuosuppressed, patients to estimate the magnitude of this risk. Then we gave our viewpoint in the perspective to screen and follow-up for active and latent chronic parasitoses, developing an hypothetical flow-chart.*

Results. *From data published in the literature the real burden of parasitoses, among patients with rheumatic diseases treated with immunosuppressive treatments, can not be estimated. Nevertheless, a positive trend on publication number exists, probably due to more than one reason: i) the increasing number of patients treated, especially with more than one immunosuppressive treatment, including new biological agents; ii) the increasing number of individuals who move from the north to the south of the world (endemic areas for parasitic infections) and viceversa, due to globalisation, and iii) the fact that more attention is paid for notification/publication of cases.*

Conclusions. *Considering parasitic infections as emerging and potentially serious in their evolution, additional strategies for the prevention, careful screening and follow-up, with a high level of suspicion, identification, and pre-emptive therapy are necessary in candidate patients for biological agents.*

Introduction

Rationale

Immunosuppressive drugs, other than corticosteroids (CS), are used in the treatment of various rheumatologic conditions to induce or maintain a remission, to reduce the frequency of flare or relapse, and to guarantee disease control. In particular, treatment options have been substantially improved in recent years thanks to the introduction of disease-modifying anti-rheumatic drugs (DMARDs), including drug-inhibiting cytokines, such as, for example, TNF-alpha antagonists, and/or blocking cytokine receptors (*i.e.* tocilizumab (TCZ), a monoclonal antibody blocking the interleukin-6 receptor). In general, these therapies seem to be acceptably well tolerated, however, taking into account the increased risk of infections, the situation is less optimistic, especially for patients treated with anti-TNF-alpha drugs (*i.e.* monoclonal antibodies, such as infliximab (IFX) and adalimumab (ADA), soluble TNF-alpha receptors, like etanercept (ETN), and others, certolizumab-pegol (CZP), golimumab (GLM), anakinra (ANA), and abatacept (ABT) (1-14), probably because of the inhibition of this crucial molecule that has a key role in the early phase of the host defense against bacterial, viral and parasitic infections (15-17). However, even data obtained before the begin-

ning of the TNF-alpha blockers era, showed an incidence rate of infections in the rheumatoid arthritis (RA) population nearly twice as high as in matched non-RA controls. Indeed, the risk of infections in rheumatic diseases can be explained with a combination of actions defined by the disease itself, with its perturbations of immune functions and impairment of general health (18), and the use of older different kind of drugs, too, that in general interfere with immune system and that are yet routinely used in these patients [*i.e.* methotrexate (MTX); cyclophosphamide (CTX); cyclosporine (CSA); azathioprine (AZA)] (18-20). The cumulative immunosuppressive activity of rheumatologic treatments, both traditional and new drugs, continues to represent one of the main factor predisposing for infections, especially in concomitant use of CS (21), with some variations related to the dose and the duration of CS treatment (22). Thus, despite different mechanisms of action, and the lack of strict correlation between a specific drug and a particular type of infection, any immunosuppressive therapy can facilitate any type of infection (23-27). In particular, many bacterial (28-44), viral (32, 45-49), and fungal (50-57) infections have been described among these patients. In addition, the impact of the parasitic diseases among rheumatic disease patients during immunosuppressive treatments, including biologic therapies, is hard to estimate since few reports exist in the literature, however, recent observations lead to consider parasitic infections as emerging in such a population (58).

Objectives

With this literature review we want to deal with the parasitosis risk among rheumatic disease patients treated with immunosuppressive drugs, including biological therapies.

For this purpose we analysed records on this topic, identified through PubMed database searching.

We also grouped the clinical cases presented in literature to estimate if the risk of parasitoses among the patient category considered actually exists and if the problem can be considered as emerging. As a positive trend on publications exists, probably also due to the recent greater attention for notification / publication of cases, but mainly to the increasing number of patients treated, especially with more than one immunosuppressive treatment, including new biological agents, and the advance of the era of globalisation with more and more people having contact with endemic areas for certain diseases, the parasitic risk seems to be emerging in such a population.

To limit the spread of this infective complication in rheumatological patients candidate for immunosuppressive agents, specific recommendations, based on a multidisciplinary contribution and a systematic review of the literature, for screening and follow-up of active and latent chronic infections have to be elaborated as happened for those caused by viruses or bacteria.

We want to give our viewpoint in the perspective of a proposition to screen and follow-up for parasites the patients undergoing immunosuppressive treatments (59).

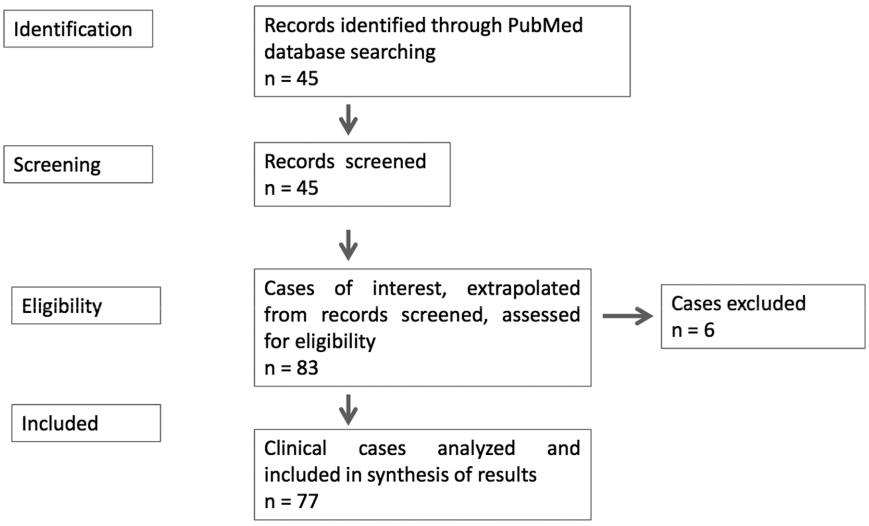

Fig. 1. PRISMA flow chart: data collection and selection of studies.

Methods

To review case reports of parasitic infections on rheumatological patients in immunosuppressive treatment, and analyse the magnitude of the data, we searched the literature on PubMed library combining the terms parasitic diseases OR parasitic infections OR parasitoses AND rheumatic diseases OR rheumatic patients AND immunosuppressive therapies OR biological DMARDs OR anti-tumour necrosis factor (TNF)-alpha. We used no language or time restrictions. The search was concluded on January 15th 2014.

Results

Study selection

We identified and screened 45 records. From these records we extrapolated 83 cases of interest assessed for eligibility. Among these we excluded only six cases with concomitant manifestation of systemic rheumatic disorders and parasitic diseases, in which no immunosuppressive treatment was administered (60, 61) (Fig. I).

Description of results

We grouped on literature reported cases of parasitic infections in rheumatic disease patients treated with immunosuppressive drugs, including biological therapies in Table I (see hereinafter).

A positive trend, probably due to i) the increasing number of patients treated, especially with more than one immunosuppressive treatment, including new biological agents, ii) globalisation, and finally iii) to higher attention for notification/publication of cases, exists. First case reports of parasitoses during anti TNF agents treatments appeared in 2003, more or less 5 years after the introduction of these drugs into the clinical practice.

Table I. Published reported cases of parasitic infections in rheumatic disease patients treated with immunosuppressive drugs, including biologic therapies, found on PubMed (60-104).

Parasitic diseases	Country of report	Pts (Age y/sex)	Rheumatologic Disease	Immunosuppressive treatments (Agents)	Treatment duration (mo) before onset of parasitic disease	Reference
Chagas disease	Brazil	43/F	RA	CS	NA	Cossermelli *et al*., 1978 (62)
	NA	1 case (y/sex NA)	SLE	NA	NA	Barousse *et al*., 1980 (61)
	NA	1 case (y/sex NA)	SLE	NA	NA	Barousse *et al*., 1980 (61)
	NA	1 case (y/sex NA)	SLE	NA	NA	Barousse *et al*., 1980 (61)
	NA	1 case (y/sex NA)	SLE	NA	NA	Barousse *et al*., 1980 (61)
	NA	1 case (y/sex NA)	SLE	NA	NA	Barousse *et al*., 1980 (61)
	Brazil	33/F	SLE	CS, CTX	NA	dos Santos-Neto *et al*., 2003 (63)
	Spain	44/F	SLE	CS, CTX	6	Pinazo *et al*., 2010 (64)
	Bolivia	40/F	SLE	CS, CTX, AM, HDX	NA	Pinazo *et al*., 2013 (60)
	Bolivia	46/F	SLE	CS	NA	Pinazo *et al*., 2013 (60)
	Argentina	44/F	SLE	CS, CTX, AZA, HDX	NA	Pinazo *et al*., 2013 (60)
Leishmaniosis	Israel	56/M	RA	MTX, CS	120	Vardy *et al*., 1999 (65)
	France	66/M	ANCA-associated vasculitis	CTX, MTX, CS	120	Zanaldi *et al*., 1999 (66)
	Italy	35/M	BD	Chlorambucil, CS	36	Sirianni *et al*., 2001 (67)
	Spain	50/M	RA	MTX, CS	120	Baixauli *et al*., 2003 (68)
	Italy	60/M	PAN	CTX, CS	2	Scatena *et al*., 2003 (69)
	Spain	55/M	PsA	IFX	9	Romani-Costa *et al*., 2004 (70)
				Others (no details given)	300	
	Italy	76/M	ANCA-associated vasculitis	CTX, CS	36	Sollima *et al*., 2004 (71)
	France	53/F	RA	IFX, AZA, CS	12	Fabre *et al*., 2005 (72)
	Italy	69/F	RA	ADA	25	Bassetti *et al*., 2006 (73)
				MTX, CS	360	
	Greece	60/F	RA	ETN	18	Bagalas et al., 2007 (74)
				CSA, CS, ANA	96	
	France	9/F	JRA	CSA, MTX, CS, ANA	60	Koné-Paut *et al*., 2007 (75)
	Italy	42/M	PsA	Efalizumab	3	Balato *et al*., 2008 (76)
	Greece	45/M	PsA	IFX, MTX, CS	60	Tektonidou *et al*., 2008 (77)
	Greece	65/F	RA	MTX	96	Venizelos *et al*., 2008 (78)
	Spain	56/F	RA	ADA	26	Balta-Cruz *et al*., 2009 (79)
	Italy	63/M	PsA	IFX	24	De Leonardis *et al*., 2009 (80)
	USA	42/F	RA	ADA	2-3	Franklin *et al*., 2009 (81)
	Spain	55/M	RA	IFX, MTX, CS	11	Garcia-Vidal *et al*., 2009 (82)
	France	7/F	JIA	ETN	11	Jeziorski *et al*., 2009 (83)
				IFX	12	
	Germany	31/M	AS	IFX	48	Mueller *et al*., 2009 (84)
	France	51/F	AS	ADA	20	Schneider *et al*., 2009 (85)
	Greece	55/M	AS	IFX, MTX	12	Xynos *et al*., 2009 (86)
	Greece	71/F	GCA	IFX, CS	24	
				MTX	12	
	France	50/M	AS	IFX	7	Hakimi *et al*., 2010 (87)
	Greece	77/F	RA	IFX	6	Kritikos *et al*., 2010 (88)
	Spain	60/M	RA	ADA	18	Moltó *et al*., 2010 (89)
		4 cases (y/sex NA)		ADA or others anti TNF-alpha (no details given)	NA	
	Spain	72/F	RA	ADA	1	Moreno *et al*., 2010 (90)
	Germany	38/M	RA	IFX	0.5	Zanger *et al*.,2011 (91)
Microsporidiosis	Brazil	38 cases (y/sex NA)	RA,AS,PsA	Combination therapy (MTX and/or AZA and/or Leflunomide and/or chloroquine and/or sulfasalazine and/or CSA) plus CS	NA	Aikawa *et al*., 2011 (92)
Norwegian scabies	NA	1 case (y/sex NA)	RA	TCZ	NA	Baccouche *et al*., 2011 (93)
Pentatrichomonas hominis infection	France*	68/M	RA	ADA, CS	NA	No Author. Rheumatology 2013 (94)
Strongyloidosis	NA	yNA/F	SLE	CS ± other drugs (no details given)	NA	Setoyama *et al*., 1997 (95)
	NA	33/F	SLE	CS	NA	Kothary *et al*., 1999 (96)
	NA	1 case (y/sex NA)	SLE	CS ± other drugs (no details given)	NA	Reiman *et al*., 2002 (97)
	NA	1 case (y/sex NA)	SLE	CS ± other drugs (no details given)	36	Lemos *et al*., 2003 (98)
	NA	69/F	RA	CS, MTX	NA	Koh *et al*., 2004 (99)
	NA	35/F	SLE	CS	NA	Arsic-Arsenijevic *et al*., 2005 (100)
	NA	1 case (y/sex NA)	RA	ETN	NA	Boatright *et al*., 2005 (101)
	NA	34/F	SLE, AS	CS, CTX	NA	Mora *et al*., 2006 (102)
	NA	37/M	AS	CS ± other drugs (no details given)	NA	Krishnamurthy *et al*., 2007 (103)
	NA	63/M	RA	Anti TNF-alpha (no details given), CS, MTX		
	Turkey	68/F	RA, BA	MTX, CS	NA	Altintop *et al*., 2010 (104)

ADA: adalimumab; AM: acid mycophenolic; ANA: anakinra; ANCA: anti-neutrophil cytoplasmic autoantibody; AS: ankylosing spondylitis; AZA: azathioprine; BA: bronchial asthma; BD: Behçet's disease; CS: corticosteroids; CSA: cyclosporine; CTX: Cyclophosphamide; ETN: etanercept; GCA: giant cell arteritis; HDX: hydroxychloroquine; IFX: infliximab; JIA: juvenile idiopathic arthritis; JRA: juvenile rheumatoid arthritis; MTX: methotrexate; NA: not applicable; PAN: polyarteritis nodosa; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; TCZ: tocilizumab *: recent travel history in Burkina Faso.

From the analysis of therapeutic schedule of the rheumatic patients reviewed, it's clear that combined treatments prevailed and that the concomitant, long-term use of different type of immunosuppressive agents certainly plays a crucial role in the development of parasitic diseases, although, at this moment, the true mechanisms at the basis of the inter-relationships remain not fully clarified.

On the basis of published data, the most represented parasitic infection in rheumatic disease patients treated with immunosuppressive drugs seems to be leishmaniosis, being strongyloidosis the second-one (see Table) (105, 106).

According to data that show increased microsporidia susceptibility and rate of dissemination in immunosuppressed patients (107-110), Aikawa *et al*. reported positive tests for microsporidia significantly higher in all types of rheumatic disease patients compared with the control subjects, and also more frequently detection microsporidia plus positive fecal leukocytes in patients than in control subjects (92).

Baccouche *et al*. described a case of Norwegian scabies in a patient with RA treated with TCZ (93), and other authors highlight as commensal non-pathogenetic agents, such as *Pentatrichomonas* (formerly *Trichomonas hominis* or *Trichomonas intestinalis*), can cause symptomatic clinical patterns (94).

Studies, analysing rheumatologic patients and comparing them with healthy people, did not find any differences for pathogenic parasites (*Entamoeba histolytica/dispar*, *Dientamoeba fragilis*, *Giardia lamblia*, *Cryptosporidium parvum*, *Cyclospora cayetanensis*, *Isospora belli*, *Ancylostoma duodenale*, *Ascaris lumbricoides*, and *Blastocystis hominis*), and non-pathogenic parasites (*Endolimax nana*, *Entamoeba coli*, and *Entamoeba hartmanni*) (92).

Although *Trypanosoma cruzi*, has not traditionally been considered an opportunistic agent, studies on experimental models (111, 112), many reports of reactivation in immunocompromised patients (mainly those with AIDS) (113-118) and some cases, reported in the scientific literature, of coexistence of Chagas disease and SLE (61, 63, 64, 60) or RA (62, 60), seem to suggest a possible role of this infection in certain category of patients, such as candidates for biological agents.

Discussion

Summary of evidence

Actually, with literature reported data, the parasitic complication, among rhematologic immunosuppressed patients, emerge as possible and increasing, but the real magnitude is not adequately appreciated.

In summary, prospective studies, to estimate the true dimension of the problem in clinical practice and to establish potential co-factors and elaborate screening programmes to study patients before initiating any immunosuppressive treatment, especially for therapeutic schedule including biological agents, and possibly introduce prophylaxis/pre-emptive therapy, are needed.

Limitations

Describing reported cases published in literature to analyse the parasitic risk during immunosuppressive rheumatological treatments, more than one limitation occurs.

First of all, it is unclear whether reported cases are primary or reactivated infections. In fact, rheumatic diseases patients could already be infected with certain parasites and develop disease only after immunosuppression status due to the therapies performed for their primary affection. For example *Strongyloides stercoralis* infection can persist in the host for several decades, and in patients who are exposed to immunosuppressive therapy this status predispose to a hyperinfection syndrome, which is characterised by a high mortality rate (119-121).

In addition to this limit, as regards the literature on this issue and in consideration of the incredible number of patients affected by rheumatic diseases and treated or undergoing immunosuppressive therapies and of the potentially "at risk" patients for primary or reactivated parasitic infection, the phenomena is certainly under-reported. More than one factor may play a role in this under-reporting. First of all, the lack of screening programmes for parasitic infections does not identify "at risk"/exposed asymptomatic patients and this leads to the low number of reported cases. Another important point regards the difficulties to diagnose and the risk for erroneous diagnosis, mainly due to the absence of any kind of symptoms or signs, and often to the lack of awareness of parasitic diseases as potential infective complication during immunosuppressive therapies also in rheumatologic patients; misdiagnosis can also come from certain parasitoses attitude to mimic rheumatologic disorders. In these circumstances, symptoms/signs presented by the patients could be completely correlated to the rheumatic disease if no screening for parasites is carried out (122). For example clinical presentation of the *S. stercoralis* hyperinfection syndrome may be variable and may mimic some features of SLE, including pulmonary haemorrhages or vasculitis (102, 123). As a consequence of these misdiagnosis of strongyloidosis, patients could receive treatment for RA or SLE developing a disseminated parasitosis because of the immunosuppressive therapies (124-133); in leishmaniosis atypical and confusing features may resemble autoimmune and systemic rheumatic diseases (see SLE) at presentation and during the course of the illness (134, 72, 135-138), and also amebosis can mimic rheumatologic diseases, but this only constitutes a differential diagnosis issue; in fact these kind of infections, at this moment, do not seem appear with greater frequency in rheumatic disease patients treated with immunosuppressing agents in general, and biological therapy in particular (139-141).

Moreover, in immunosuppressed patients the possibility of atypical presentation of infectious diseases (including the parasitic ones) is frequent, because of the immune status in general and the specific therapies for the rheumatic disorders (72, 142); in this regard, especially TNF-alpha-blocking treatment may mask the typical symptoms of infectious diseases, constituting an additional confounding factor.

Perspectives

The Authors' viewpoint in the perspec-

tive to screen and follow-up active and latent chronic parasitoses is a proposal for a flow-chart. As many parasitic infections are clinically silent, a detailed interview to rheumatic disease patients undergoing immunosuppressive treatments should be performed to assess the presence of epidemiological (citizen status, living conditions, and positive travel history) and clinical (comorbidities, treatments with any type of pharmacological agents, previous blood transfusions and/or stem cell or solid organ transplantation), and patient-specific (alcohol and/or drug abuse) risk factors that could act as co-factors in the development of infective complications. In fact, epidemiological factors, such as past residence in tropical and subtropical regions, and certain personal behaviors with low levels of hygiene conditions or certain not fully standardised methodologies to screen donors, especially those with a not clear history of contacts with and/or travels to endemic regions for parasites, could facilitate exposition to parasitic agents, and, together with comorbidities, pharmacologic agents or toxic substances, with immunosuppressive effects, could increase the risk for the development of more severe disease in case of parasitic primary infection/reactivation.

After anamnesis and physical examination, blood exam for chemistry and full blood count should be done. Eosinophilia might be a potential marker to look further in screening for some parasites in asymptomatic individuals, and in particular for chronic strongyloidosis (143-145), not forgetting that its absence does not absolutely exclude a parasitic infection (146-149), also because it might be often intermittent (150, 151).

All patients have to give several stool sample, too, to perform microscopic examination and if necessary also coproculture.

Blood samples, especially in populations from endemic areas with potential parasites-exposure history, should also be screened serologically for strongyloidosis and leishmaniosis, in particular. Serology in strongyloidosis appears the most reliable and sensitive screening procedure especially in populations from *Strongyloides*-endemic areas. Regarding leishmaniosis, data in favour of the ability of the serological analysis alone to screen for leishmaniosis before initiation of biological or immunosuppressive treatments are lacking. Evidence indicates that serological analysis can identify only symptomatic or asymptomatic cases with recent and still active infection (152, 153). Thus, considering that especially in leishmaniosis-endemic countries, where asymptomatic visceral leishmaniosis (VL) infections occur more frequently than clinically apparent VL cases, leishmanin skin test (LST) (Montenegro test) appears to be the only screening test capable of detecting asymptomatic *Leishmania* infections. A positive LST result is thought to indicate durable cell-mediated immunity after asymptomatic infection or clinical cure of VL (154) and VL with unusual signs and symptoms may develop in immunocompromised patients with previous LST positivity after immunosuppressive treatments. Cascio and Iaria (155) suggest LST along with serologic analysis; Pizzorni *et al*. recommend serological monitoring for leishmaniosis must be carried out in individuals that live in endemic areas during therapy with anti-TNF monoclonal antibodies, since cytokine-induced macrophage activation and tissue granuloma formation essential to control infection, are inhibited during the use of this medication (156).

No data are present in the literature regarding *T. gondii*, but on the basis of the risk of reactivation, serology should be performed at regular interval (13). Prevention measures and re-testing at regular interval, too, should be indicated for negative patients for the risk of more severe primary infections during immunosuppression.

Thus in "at risk" patients for epidemiological and / or clinical patient-specific factors (*i.e*. origin or travels in endemic countries, blood transfusions or stem cells or solid organ transplantations), it could be indicated also serology for trypanosomosis.

The performance of an accurate screening "flow chart" (Fig. 2) appear even more indicated especially considering that prophylaxis and pre-emptive treatment for parasitoses mentionated before are available.

Nevertheless, few data exist on the use of anti-*Leishmania* therapies for LST-positive or serologically positive patients (155).

Instead, *S. stercoralis* complete eradication before the initiation of immunosuppressive therapy is essential in

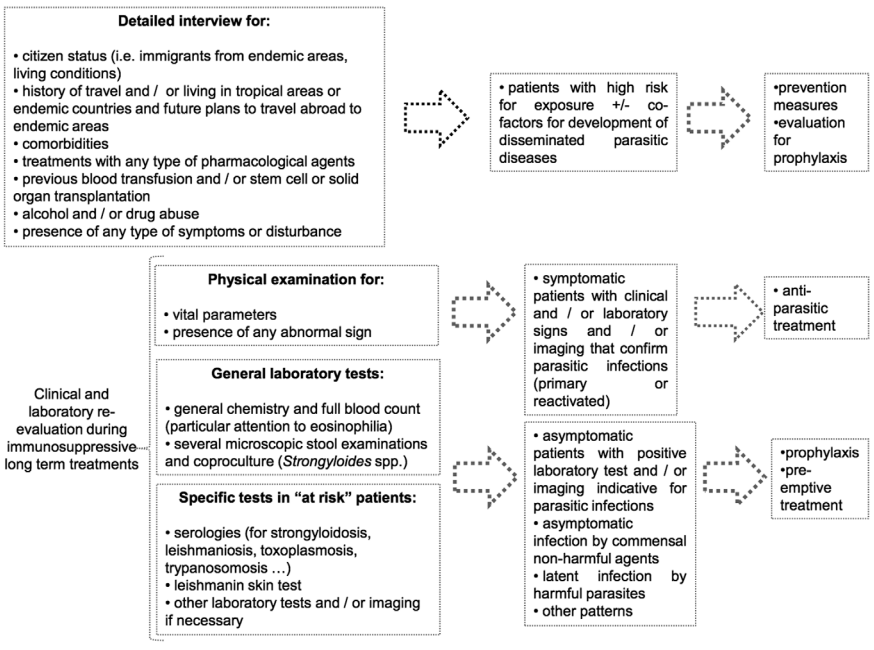

Fig. 2. A hypothesis of a "flow chart" to screen and follow-up for parasites rheumatic disease patients undergoing immunosuppressive treatments.

patients with uncomplicated infections to ensure that hyperinfection syndrome does not develop (102). In general, falling eosinophilia and *Strongyloides* antibody titers are indications of successful treatment (157). Thus, a systematic pre-emptive course of ivermectin (one to two days) is strongly recommended before any immunosuppressive treatment in 'at-risk' patients with potential *Strongyloides*-exposure history (*i.e.* having stayed in tropical areas even for a short period and even decades ago) (158, 119) and/or with demonstrated chronic, asymptomatic infection.

For Chagas disease caused by *Trypanosoma cruzi*, despite a lack of evidence-based data, treatment with benznidazole or nifurtimox should be initiated before immunosuppression with the aim to reduce the effects of a possible reactivation. Timely antiparasitic treatment with benznidazole and nifurtimox (or with posaconazole in cases of therapeutic failure) has proven to be highly effective in preventing Chagas disease reactivation, although such treatment has not been formally incorporated into management protocols for immunosuppressed patients. International consensus guidelines based on expert opinion would greatly contribute to standardising the management of immunosuppressed patients with Chagas disease (60).

The prophylactic use of anti-helminthic drugs is recommended for patients under concomitant glucocorticoid therapy and it could be extended to those initiating anti-TNF therapy (158).

In general, at present, no guidelines exist, and whether these approaches will be adopted remains an open and important question.

Conclusions

Screening of rheumatic disease patients for some infectious agents, such as tuberculosis, HIV and viral hepatitis, is now mandatory before starting immunosuppressive therapies, DMARDs in particular, but, for the moment, no indication exists for parasitosis risk. On the basis of epidemiological data and immunopathological aspects, guidelines for screening and treatment of parasitoses for rheumatic disease patients, especially if undergoing TNF antagonists, are needed (159).

Some National Societies such as the Italian and Spanish Societies of Rheumatology (SIR and SER) and Tropical Medicine (SIMET and SEMTSI) are starting to plan specific recommendations, based on a multidisciplinary contribution and a systematic review of the literature, to screen and follow-up active and latent chronic infections, including parasitoses, in candidate patients for biological agents, in consideration of epidemiological factors such as for example, the patient's place of birth, habits, etc. (59).

Indeed, today, also in Europe, a continued and growing number of patients are "at risk" for parasitoses by virtue of their country of origin, travel habits, and living conditions (160); this should lead to modifications of the physician's habits before initiation and during rheumatic disease treatments, especially for treatment with biological agents. . It could also be useful to monitor and re-test "at risk" patients at regular intervals during long-term immunosuppressive treatment, even taking into account that some laboratory parameters could be insignificant because of immunosuppression status.

All these elements, taken together, make diagnosis of certain parasitic diseases very difficult. Thus, a high degree of suspicion is needed, and an extensive diagnostic work-up must be warranted.

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