Review

Recommendations for the management of pulmonary fungal infections in patients with rheumatoid arthritis

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ABSTRACT

Often life-threatening pulmonary fungal infections (PFIs) can occur in patients with rheumatoid arthritis (RA) receiving disease-modifying anti-rheumatic drugs (DMARDs). Most of the data concerning PFIs in RA patients come from case reports and retrospective case series. Of the five most widely described PFIs, Pneumocystis jirovecii pneumonia (PJP) has rarely been seen outside Japan, pulmonary cryptococcosis has been diagnosed in only a small number of patients worldwide, pulmonary coccidioidomycosis has almost only been observed in endemic areas, the limited number of cases of pulmonary histoplasmosis have mainly occurred in the USA, and the rare cases of invasive pulmonary aspergillosis have only been encountered in leukopenic patients. Many aspects of the prophylaxis, diagnosis and treatment of PFIs in RA patients remain to be defined, as does the role of each DMARD in increasing the risk of infection, and the possibility of resuming biological and non-biological DMARD treatment after the infection has been cured. The recommendations for the management of PFIs described in this paper are the product of a consensus procedure promoted by the Italian group for the Study and Management of Infections in Patients with Rheumatic Diseases (the ISMIR group).

Introduction

The increasing number of immunocompromised patients and improvements in diagnostic methods have led to an increase in the number of diagnoses of invasive pulmonary fungal infections (PFIs) (1). These have also been described in patients receiving biological tumour necrosis factor (TNF)-α inhibitors (TNFIs) (2-4), although the findings of meta-analyses of randomised controlled trials (RCTs) indicate that the real risk of opportunistic fungal infections is not very high. Bongartz *et al*. reported one case of histoplasmosis and one of coccidioidomycosis among 126 serious infections in patients with rheumatoid arthritis (RA) treated with infliximab or adalimumab (5), and a meta-analysis of 70 trials found a 1.7 excess risk of infections per 1000 patients treated with biological drugs due to a significantly increased risk of mycobacterial and viral infections, but not invasive fungal infections (4). Nevertheless, PFIs are often life-threatening, and many aspects of their prophylaxis, diagnosis and treatment in the particular setting of RA patients remain to be defined, as does the possibility of resuming treatment with disease-modifying anti-rheumatic drugs (DMARDs) after infection. For these reasons, the **I**talian group for the **S**tudy and **M**anagement of the **I**nfections in Patients with **R**heumatic Diseases (the **ISMIR** group) endorsed a national consensus process to review the available evidence and produce practical, hospital-wide recommendations.

Methods

The criteria of the Oxford Centre for Evidence-based Medicine (http://www.cebm.net/ index.aspx?o=1025) were used to assess the quality of the

evidence and the strength of the recommendations.

Search strategy

The studies included in the evaluation had to be RCTs, observational studies (*i.e.* cross-sectional, non-interventional case-control or cohort studies), systematic reviews or case reports evaluating the risk of infections, opportunistic infections, and fungal infections in patients exposed to biological DMARDs (bDMARDs). A search was made of the MEDLINE and EMBASE databases from 1998 to May 2016 using the key words: "rheumatoid arthritis" or "arthritis" or "arthritides" or "polyarthritis" and "anti-TNF drugs" or "anti-TNF agents" or "anti-TNF therapy" or "anti-TNF blockers" or "infliximab" or "etanercept" or "adalimumab" and "fungal pulmonary infections", "lung infections" "opportunistic infections" or "*Pneumocystis jirovecii* infection", *"Cryptococcus neoformans* pulmonary infections" "*Coccidioides immitis* pulmonary infections" "*Histoplasma capsulatum* pulmonary infections", "*Aspergillus* pulmonary infections". There were no restrictions on publication status. The diagnosis of RA in the considered studies was made on the basis of the 1988 American College of Rheumatology (ACR) and ACR/European League Against Rheumatism (EULAR) criteria (6, 7); a diagnosis made after a clinical examination by a rheumatologist was also considered acceptable. Studies including subjects aged <18 years were discarded. This analysis considered the PFIs occurring in patients treated with bDMARDs or synthetic DMARDs (sDMARDs).

Pneumocystosis

Pneumocystis jirovecii (formerly known as *Pneumocystis carinii*) is a species-specific opportunistic pathogen classified as a fungus in the phylum Ascomyceta (8, 9). *P.jirovecii* pneumonia (PJP) can occur in deeply immunosuppressed patients (10-13), including RA patients in whom it can cause sudden and severe respiratory failure and death (14, 15). Before the introduction of bDMARDs, some cases of PJP were reported in patients who had been treated with methotrexate (MTX) and steroids for a long time (16-18). TNF-α inhibition affects host defences against *P.jirovecii* infection in animal models (19-21) but, even after the introduction of bDMARDs, PJP remained an infrequent finding in RA patients in the USA and Europe (22-25).

A prospective study of the British Society for Rheumatology compared 13,905 patients treated with TNFs and 3,677 treated with sDMARD, and identified 17 cases of PJP cases: the incident rates were 0.2/1000 person-years of follow-up (95% confidence interval [CI] 1.2-3.3) in the TNFI cohort, and 0.11/1000 person-years follow-up (95% CI 0.3, 4.3) in the sDMARD cohort. The age-adjusted hazard ratio for PJP infection in the TNFI-treated patients was 2.3 (95% CI 0.5-10.1) (26). The situation seems to be different in Japan, where a total of 243 PJP cases had been reported in patients receiving MTX up to 2012 (15), and the post-marketing surveillance programme identified 16 cases in 7,091 patients receiving etanercept (0.23%) (27), 22 cases in 5,000 patients receiving infliximab (0.4%) (28), nine cases in 3,000 patients receiving adalimumab (0.3%) (29), and five cases in 3,881 patients receiving tocilizumab (0.28%) (30). Worldwide reports of PJP in RA patients receiving golimumab (15,31) and certolizumab pegol (32), or other biological drugs such as abatacept (15) and rituximab (33-36) are scarce and mainly anecdotal. The higher incidence of PJP in Japanese RA patients remains unexplained.

It is also unclear whether the use of bDMARDs rather than conventional treatments increases the risk of PJP, although one meta-analysis found no difference in the incidence of PJP between RA patients receiving bDMARDs and sDMARDs (mainly MTX) (4). Corticosteroid therapy can reduce the number and function of $CD4^+$ T cells and thus increase the risk of PJP (10, 37-45), and it is known that $CD4^+$ T cell counts of <200/μL are associated with the development of PJP in rheumatic patients (46, 47), although it may also occur at higher CD4 counts (14, 37, 41, 46, 48). It has been found that lymphopenia (<500/μL) during corticosteroid therapy (45), lymphocyte counts of <1500/μL, and serum IgG levels of 1000 mg/dL (37) predict PJP infection in patients with rheumatic diseases. Komano *et al*. (49) found significantly lower levels of serum IgG and albumin in patients with PJP than in those without, and claimed that PJP was predicted by age (>65 years), prednisolone dose (≥6 mg/day), and pulmonary comorbidities, the role of which has since been confirmed (50).

In the British study mentioned above, the median time to PJP infection after starting TNFI treatment was 5.8 months (interquartile range 2.7–16.8) (26). The presentation of PJP in RA patients is preceded by variable degrees of fatigue and respiratory symptoms (15). Chest radiographs may be almost normal, but high-resolution CT scans can reveal diffuse ground-glass opacities without the interlobular septal boundaries typical of MTX-related interstitial pneumonia (13). The poor prognosis of PJP in RA patients has been associated with an older age, high 1-3β-d-glucan levels, the use of MTX, hypoxaemia, bilateral lung findings, the need for mechanical ventilation, and low lymphocyte counts (37). It has been suggested that Japanese patients treated with bDMARDs are at increased risk of death (15), particularly those with pre-existing pulmonary lesions (51).

As *P. jirovecii* cannot be cultured, diagnosis of the infection relies on detecting it by means of optical microscopy in lung tissue or bronchoalveolar lavage (BAL) fluid. Searches in induced sputum are burdened by a high rate of false negative results (52) and, although the polymerase chain reaction (PCR) analysis of induced sputum is more sensitive, the method is not generally available in clinical practice. At the time of the introduction of TNF-α blocking agents, determining serum 1→3-β-d-glucan levels (52, 53) was recommended in the Japanese guidelines for RA patients (54) but, in addition to being expensive, this test is pan-fungal and not specific for *P. jirovecii*.

The development of PJP in immunocompromised patients seems to be due to *de novo* infections, and the most likely way RA outpatients acquire the

infection is person-to-person transmission, and it has suggested that outpatient clinic waiting rooms may also play a role (15). The role of PJP prophylaxis in RA patients remains controversial. Universal routine prophylaxis is considered impracticable because of the long-term nature of anti-RA therapy (15), and it is known that PJP can occur after the discontinuation of primary prophylaxis in RA patients with lymphopenia (55, 56). A meta-analysis of studies of HIV-negative immunocompromised patients has shown that trimethoprim/sulfamethoxazole (TMP/SMX) prophylaxis is highly effective but it should only be considered whenever the risk of developing PJP is higher than the rate of adverse events associated with TMP/SMX administration (3.1% among adults) (57). It is therefore generally not recommended in RA patients (58), although the Japanese Ministry of Health recommendations (59) suggest short-term primary prophylaxis with TMP/SMX at a daily dose of 80-400 mg for 5–7 days (or two tablets three times a week) for all RA patients scheduled to start biological and/or non-biological anti-rheumatic therapy (60). Blood dyscrasia has been reported in patients simultaneously taking MTX and TMP/SMX at the standard therapeutic dose (61, 62), and so the use of TMP/SMX in patients treated with MTX is not recommended in the Canadian Initiative in Rheumatology guidelines (62).

TMP/SMX is the treatment of choice for *P. jirovecii* infections of any severity (1, 52). In the case of mild disease, oral TMP/SMX can be given at a dose of two double-strength tablets (160 mg of TMP and 800 mg of SMX) every eight hours. In severe cases, the drug should be administered intravenously at a TMP dose of 15-20 mg/kg and an SMX dose of 75-100 mg/kg every 6-8 hours. The alternative treatments for patients who are either intolerant or hypersensitive to TMP/SMX are intravenous pentamidine or intravenous clindamycin plus oral primaquine (52). High-dose corticosteroids greatly improve PJP outcomes in HIV-infected patients (63). It must also be remembered that the discontinuation of corticosteroid therapy in patients developing PJP can lead to lung damage as a result of immune reconstitution (64).

P. jiroveci disappears after 7-10 days of TMP-SMX treatment in most cases (65), and no relapse of PJP was seen during an average follow-up of 22 months in patients treated with TMP/SMX for a mean of 17 days, even though they continued to receive immunosuppressants for their rheumatic diseases without secondary prophylaxis (39).

Questions and statements

When should PJP be suspected in RA patients?

PJP should enter in the differential diagnosis of interstitial disorders of the lung in RA patients. ***CII***

Should patients with RA receive primary PJP prophylaxis?

PJP prophylaxis should be prescribed to patients with a CD4 cell count of <200 /µL or a lymphocyte count of <500µL, while carefully monitoring untoward effects. ***BII***

Patients presenting three or more potential risk factors (an age of >65 years, a lymphocyte count of >500 µL<1500µL, exposure to immunosuppressants and/or corticosteroids for >3 years, previous exposure to another biological drug, lung comorbidities, below normal serum albumin or serum IgG levels) merit particular attention, and can be considered for primary PJP prophylaxis on a case-by-case basis. ***CIII***

What should be done if a patient is diagnosed with PJP?

The immediate withdrawal of corticosteroid therapy is not appropriate. On the contrary, intensification with high-dose corticosteroids should be considered during the acute phase of the disease. ***BII***

It is appropriate to discontinue MTX, particularly in the case of serious infections requiring high-dose intravenous TMP/SMX. ***CIII***

The discontinuation of bDMARDs should be considered in all patients, particularly in the case of lymphopenia or low CD4⁺ lymphocyte counts. ***DIII***

Is re-treatment with bDMARDs possible in PJP survivors?

After the complete resolution of PJP symptoms and the completion of TMP/SMX treatment, re-treatment with bDMARDs can be considered on a case-by-case basis. Secondary prophylaxis with TMP/SMX or pentamidine during re-treatment with bDMARDs can also be considered, particularly in lymphopenic patients. ***DIII***

Cryptococcis

Cryptococcosis is a fungal infection caused by two species of yeast: *Cryptococcus neoformans* and *C. gattii* (66). *C. neoformans* infection is observed worldwide mainly in immunocompromised patients (67, 68); however, approximately 20% of the patients with a diagnosis of cryptococcosis have no apparent risk factor or underlying disease. *C. gattii* infection mainly occurs in immunocompetent hosts in endemic tropical regions, but it has also recently been reported in Vancouver Island (British Columbia) and the Pacific North-west of the USA (69).

Primary cryptococcal infection occurs in the lung following the inhalation of dried yeast cells or basidiospores from an environmental source such as avian guano, soil and trees. The disease may remain localised or disseminate through the bloodstream to the central nervous system (CNS) and invade the leptomeninges (67).

Pulmonary cryptococcosis was first described in MTX-treated RA patients in 1987 (70), and the first disseminated infection in an RA patient treated with infliximab and MTX was reported in 2002 (71). Up to 2008, 28 cases of TNFI-associated *Cryptococcus* infection had been reviewed (2). Analysis of the FDA's Adverse Event Reporting System (AERS) database from 1998 to the third quarter of 2002 showed that the incidence of cryptococcosis was similar in American patients treated with infliximab ($5.1/10^5$) or etanercept ($7.1/10^5$) (72), whereas no cases of cryptococcosis were detected in the 10,050 patients treated with adalimumab included in the US post-marketing database (73). However, four cases of cryptococcosis (two with pulmonary infections) were reported in 1,080 Spanish patients treated with adalimumab between 2003 and 2006 (74-76). Pulmonary cryptococcosis has also been

described in Japanese patients treated with corticosteroids and MTX including one receiving infliximab (77) and one treated with MTX and adalimumab (78). However, no cases were reported among more than 30,000 patients treated with bDMARDs enrolled in the 70 RCTs included in the meta-analysis of Kourbeti *et al*., and only one case was detected among the control patients (4). Taken together, the available data do not indicate any significant difference in incidence of cryptococcosis depending on what bDMARD is used, or between patients treated with biological or non-biological drugs.

Computed tomography (CT) reveals nodules in 80% of RA patients with pulmonary cryptococcosis, consolidation in 30%, and cavitary lesions in 10%. Among the patients treated with TNFIs, the diagnosis was made on the basis of a biopsy or surgery in five cases (71, 75, 78-80) and by means of bronchoalveolar lavage in the others (81, 82). The serum cryptococcal capsular antigen test is highly sensitive and specific in the context of meningitis in other immunocompromised hosts (83), and was positive in 57% of RA patients with disseminated disease and pulmonary involvement (71, 80, 84, 85) and in about 40% of those with pulmonary infection alone (75, 79-81). In the presence of rheumatoid factor, false positive cryptococcal capsular antigen test results have been recorded in serum and cerebrospinal fluid (86), but these can be avoided by pre-treating serum with pronase or boiling it with EDTA for five minutes. Although the majority of patients so far described did not undergo a lumbar puncture to rule out meningitis, this is recommended in immunocompromised hosts because the fungus has a high propensity to disseminate (67, 85). In sub-Saharan Africa, where the burden of cryptococcal meningitis in HIV patients is the highest in the world, the use of the newly available lateral flow assay for the detection of cryptococcal antigen has been shown to be cost-effective (87, 88).

There are no specific recommendations regarding screening and prophylaxis for cryptococcus infection in patients receiving TNF-α blockers. All but one of the reported RA patients with pulmonary cryptococcosis were treated with amphotericin B dehoxycholate or fluconazole, followed by fluconazole maintenance therapy (71, 75, 80-84). According to the guidelines of the Infectious Diseases Society of America, immunocompromised patients with pulmonary cryptococcosis should be treated with fluconazole 400 mg/day for 6–12 months in the case of mild-moderate symptoms, whereas treatment such as that used for CNS disease is recommended in the case of severe pneumonia (89). The recommended regimen for HIV-negative transplantation patients is amphotericin B dehoxycholate 0.7-1 mg/kg/day plus flucytosine 100 mg/kg/day for at least four weeks, followed by consolidation with fluconazole 400-800 mg/day for eight weeks, and 6–12 months of maintenance therapy with fluconazole 200 mg/day (89). Although it has not been demonstrated that liposomal amphotericin B (L-AMB) is more efficacious than the dehoxycholate formulation, a number of guidelines and experts recommend it as first-choice therapy because it is less nephrotoxic (90-92). In the transplant setting, the use of L-AMB regardless of renal dysfunction has been suggested because it has less pro-inflammatory activity than the dehoxycholate formulation (90-93). All of the patients so far described discontinued TNF-α blocker agents, and the treatment was resumed in only one case (80).

Questions and statements

When should pulmonary cryptococcosis be suspected?

Pulmonary cryptococcosis enters in the differential diagnosis of lung disorders in severely immunocompromised patients presenting nodular, consolidated or cavitary lesions of the lung. ***BI***

What should be done in the case of patients with pulmonary cryptococcosis?

DMARD treatment should be discontinued. CIII

Is re-treatment with biological DMARDs possible in survivors?

It is currently unknown whether or not a patient with previous cryptococcosis can be safely re-treated with biological DMARDs. Most of the experts on the panel consider it unwise. ***CIII***

Coccidiodomycosis

Coccidiodomycosis can be caused by two closely related dimorphic fungi: *Coccidioides immitis* and *C. posadasii* (94). *Coccidioides* species are endemic in the west and south-western part of the USA (particularly Arizona, California, Nevada, Texas and New Mexico), as well as in desert areas of Central America (Mexico, Guatemala and Honduras) (95) and South America (Argentina, Bolivia, Brazil, Paraguay and Venezuela) (94). The majority of cases are acquired by inhalation, and approximately 60% of the infections are asymptomatic. The infective forms are arthroconidia (or spore), which can remain viable for many years in soil under dry conditions.

Three hundred and forty-five cumulative cases of coccidiodomycosis were identified in a random 5% sample of USA Medicare data from 1999 to 2008, including 21 patients (6.1%) with concomitant RA (95). A retrospective study of patients observed between January 2000 and June 2006 in Arizona revealed a diagnosis of coccidiodomycosis in 3.1% of RA patients, and in 14.3% of those with ankylosing spondylitis (94). Among patients receiving TNFIs in endemic areas, the use of infliximab was associated with a 5.23 relative risk of coccidiodomycosis (CI 95% 1.54–17.71) in comparison with other medications, and a significantly increased risk persisted even after adjusting for age and the use of MTX and prednisone (95).

Pulmonary involvement has been observed in 66–100% of coccidioidomycosis cases diagnosed in patients with rheumatic diseases treated with immunosuppressive drugs (96-99). Some cases of lethal disseminated disease have been described (96-100), although exclusively pulmonary involvement has been found in 66–81.8% of patients. Rheumatic symptoms accompanying acute pulmonary disease can cause a clinical picture known as “desert rheumatism”, which may lead to more aggressive treatment of the underlying rheumatic syndrome, sometime with serious consequences for the patient (98). The prevalence of coccidiodomycosis in endemic areas is 1.1–9% (96-98), with incidence rates of 1% in the

first year after the diagnosis of RA, and 9% during the first five years after diagnosis, and respectively 2% and 12% one and five years after starting infliximab therapy (96). The risk is virtually absent in patients living in non-endemic areas, where the only reported RA case of pulmonary coccidioidomycosis occurred in a patient treated with infliximab who probably inhaled rock dust imported from Arizona (101).

Most cases of coccidioidomycosis have been diagnosed serologically, and some by means of cultures or histopathological demonstration (97, 102). Taroumian *et al*. made a definite diagnosis of pulmonary coccidioidomycosis by means of histology or culture in about 15% of their patients, but in all of those with disseminated disease, whereas serological tests (enzyme immunoassay, immunodiffusion or complement fixation) detected a previous asymptomatic infection in 14% (98). Some authors recommend that patients living in endemic areas should undergo a chest radiography and specific serological tests before starting TNFI therapy (103, 104), and a serological test every 3–4 months (105).

Azole prophylaxis has been suggested in patients treated with TNFIs who live in endemic regions . Immunocompromised patients with pulmonary coccidioidomycosis should be treated with an azole (fluconazole or itraconazole 400 mg/day) for 3–6 months or longer, depending on their clinical response (1). In the presence of lung cavities, the duration of antifungal therapy should be extended to 12–18 months. Patients presenting with primary coccidioidomycosis and signs or symptoms indicating possible CNS involvement should undergo a lumbar puncture to exclude meningitis. This is especially important as coccidioidomycosis meningitis should be treated with fluconazole 400–1000 mg/day or itraconazole 400–600 mg/day for life. The use of amphotericin B is generally reserved for the induction treatment of severe pulmonary or disseminated (non-meningeal) disease (1).

Fifty-nine percent of the patients in the retrospective study of Taroumian *et al*. stopped both sDMARDS and bDMARDs at the time coccidioidomycosis was diagnosed, 18% only stopped bDMARDs, and 22.7% continued their ongoing immunosuppressive treatment. The drugs were continued or had been resumed by 87% of the patients after a median follow-up of 12 months (range 1–72 months) (98). Most of the patients (93%) received antifungal therapy (usually fluconazole 400 mg/day), the median duration of which was 12 months (range 0–96 months).

A history of CNS infection is generally considered a contraindication to the resumption of DMARDs. In the other cases, fluconazole maintenance therapy is suggested if bDMARD therapy is resumed (100).

Questions and statements

Is any specific bDMARD associated with an increased risk of coccidioidomycosis ?

The use of infliximab is associated with an increased risk of symptomatic coccidioidomycosis. ***CII***

Are any specific interventions recommended before or during TNFI treatment?

Chest radiography and coccidioidal serology (IgM/IgG) are generally recommended in endemic areas before starting TNF-α antagonist treatment. ***CIII***

What should be done in the case of patients with pulmonary coccidioidomycosis? Is re-treatment with biological DMARDs possible in survivors?

Immunosuppressive therapy should be stopped when coccidioidomycosis is diagnosed, but its resumption can be considered on an individual basis accompanied by fluconazole maintenance therapy. ***DIII***

Histoplasmosis

Histoplasmosis is an endemic mycosis caused by two varieties of the dimorphic fungus *Histoplasma capsulatum* (Hc): *Hc var*. *capsulatum* in Mid-western and South-eastern areas of the USA, Latin America, Asia (China, India, Myanmar and Thailand), and Africa; and *Hc var*. *duboisii* in Africa (106). Outside these endemic areas, histoplasmosis is generally an imported infection, although small foci of autochthonous histoplasmosis have been described in Italy (mainly in Lombardy and Emilia-Romagna) (107, 108). However, the fungus is probably more widespread than previously thought, and some experts recommend considering a diagnosis of histoplasmosis in all febrile and immunosuppressed patients, regardless of their geographical location or travelling history (109, 110). The natural habitat of the fungus is soil with a high nitrogen content, particularly in areas contaminated by bird or bat guano. Many of the described cases involve activities associated with soil excavation, building or renovation work, or visits to bat caves. Once inhaled, the mycelial form transforms itself into the pathogenic yeast in the lungs, and causes a wide range of clinical manifestations, including acute pulmonary infection or disseminated disease in about 5% of cases (mainly immunocompromised subjects) (106).

Histoplasmosis was first reported in RA patients in 2002 and, soon after, two case series from endemic areas of the United States highlighted its severe and life-threatening nature (111-113). The FDA's AERS database reported 42 cases of histoplasmosis between 1998 and 2002, with a six-fold higher ratio in patients treated with infliximab (39/233,000) than in those treated with etanercept (114). In the Mayo Clinic case series, 26 RA patients developed histoplasmosis over a period of eleven years (115): 81% were receiving MTX, 58% TNFIs, and 58% corticosteroids. The lung was the only site of infection in 54% of the patients, and 75% of the patients with disseminated disease had lung involvement. Antifungal therapy was administered to 92% of the patients, nine of whom (35%) received an initial L-AMB course (115). Hage *et al*. at Indiana University (116) found that 89% percent of the 19 patients who developed histoplasmosis while receiving TNFIs had disseminated disease (as is usual among immunocompromised hosts), and 79% showed lung involvement. A multicentre retrospective review of 98 patients diagnosed with histoplasmosis (including 52 patients with RA), 67.3% of whom were being treated with infliximab, found that concomitant corticosteroid use (OR 3.94,

Table I. Suggested screening for opportunistic pulmonary fungal infections before administering a biological DMARD to RA patients.

Pneumocystosis:	Consider total leukocyte count at baseline, and CD4 lymphocyte count in patients previously exposed to several DMARD combinations.
Cryptococcosis:	Consider chest radiography and serum cryptococcal antigen testing at baseline.
Histoplasmosis:	In endemic areas, consider chest radiography and urine histoplasmin antigen testing at baseline, and follow-up urine antigen testing every 3-4 months.
Coccidioidomycosis:	Chest radiography and serological IgM and IgG testing at baseline. Consider follow-up testing every 3-4 months for patients living in endemic areas.
Aspergillosis:	Consider absolute neutrophil count at baseline.

95% CI 1.06–14.60) and higher urine histoplasma antigen levels (OR, 1.14, 95% CI, 1.03–1.25) were independent predictors of severe disease. Two of the RA patients experienced a recurrence: one after eight months (two months after resuming adalimumab), and one after 14 months while still without biological drug treatment (117).

Transbronchial or open lung biopsies were used to diagnose 80% of the patients with histoplasmosis taking TNFIs (112). It has been suggested that the diagnostic work-up of symptomatic patients should include two or more blood cultures, and testing for *Histoplasma* antigenuria and antigenemia (116). The sensitivity of the *Histoplasma* antigen assay is 95% in patients on TNFIs (116), but the test is generally unavailable outside the USA. Serum *Aspergillus* galactomannan antigen test gives false-positive results in patients with disseminated histoplasmosis, and might be considered a surrogate diagnostic marker when no specific antigen test is available (118, 119). However, serum galactomannan antigen levels can be non-specifically high in patients with RA (120). Bronchoscopy with BAL and a biopsy are generally indicated for the diagnosis of pulmonary histoplasmosis, and specimens should be cultured and appropriately examined microscopically in order to identify the fungal pathogen. When available, the *Histoplasma* antigen test can also be used on BAL fluid. According to the most recent Infectious Diseases Society of America (IDSA) guidelines, antifungal treatment is indicated for all patients (121). The recommended treatment regimen is itraconazole 200 mg three times daily for three days, followed by 200 mg twice daily for 12 months if the disease is mild or moderate; in patients with moderately severe or severe acute pulmonary histoplasmosis, it is an intravenous lipid formulation of amphotericin B (3–5 mg/kg/day for 1–2 weeks), followed by itraconazole 200 mg three times daily for three days, and then 200 mg twice daily for 12 weeks (1, 121). Monitoring itraconazole levels is generally recommended because they vary widely from patient to patient. In the patients described by Vergidis *et al*., antifungal treatment was continued for a median of 11 months (range 3–27 months), and the median follow-up was 32 months (range 1–120 months) (117). The authors suggested that antifungal therapy can be discontinued after 12 months in patients who do not resume TNFIs. The FDA recommends discontinuing TNFIs in patients with a presumed or definite diagnosis of systemic fungal infections (122). Hage *et al*. (116) observed immune reconstitution inflammatory syndrome (IRIS) in 42% of the patients stopping TNFIs, but Vergidis *et al*. observed it in only two

Table II. Invasive pulmonary fungal diseases in RA patients treated with DMARDS: frequency and management.

Fungal disease	Frequency	Most frequently involved drugs[§]	Should DMARD treatment be discontinued?	Immune reconstitution syndrome	Can DMARDs be resumed after clinical resolution of fungal disease?
Pneumocystosis	Rare (except in Japan)	MTX and/or infliximab	Yes (possible steroid intensi-fication in acute phase of PJP)	Possible in patients abruptly discontinuing corticosteroid treatment	Consider case-by-case (not recommended in the presence of lymphopenia or low CD4 cell count). Consider secondary prophylaxis with TMP/SMX
Cryptococcosis	Rare	None	Yes	Reported in one case (74)	Insufficient data, probably very hazardous
Coccidioidomycosis	Rare (only seen in the Americas)*	Infliximab	Yes	No data	Consider case-by-case, with fluconazole maintenance therapy
Histoplasmosis	Rare in Europe;** more frequent in the USA	Infliximab	Yes	Reported in 9% of cases (125)	Consider in patients with undetectable antigen levels and no signs of residual disease after prolonged anti-fungal therapy (≥12 months)
Aspergillosis	Very rare (only seen in neutropenic patients)	None	Yes	No data	Consider after reversal of neutropenia

[§]Statistical significance is not reached in any case
*In Europe, consider patients who have travelled to highly endemic areas.
**Consider in patients who have travelled to highly endemic areas; some autochthonous cases observed in Northern Italy (110, 111).

of their 52 patients (3.8%) (117). Furthermore, 25 of 74 patients (33.8%; the number of RA patients was not specified) resumed bDMARDs after a median of 12 months (range, 1–69 months). It has been suggested that patients resuming TNFI therapy should continue to receive itraconazole for as long as they are on treatment (123).

Questions and statements

Is any specific bDMARD associated with an increased risk of developing pulmonary histoplasmosis?

The risk of pulmonary histoplasmosis seems to be higher in patients treated with infliximab. ***DIII***

What should be done in the case of patients who have pulmonary histoplasmosis?

Discontinuing immunosuppressive therapy should always be considered. If discontinued, monitor for IRIS. ***DIII***

Is re-treatment with biological DMARDs possible?

Resuming immunosoppressive treatment (including bDMARDs) can be considered after treatment with antifungal drugs for ≥12 months in patients who are Histoplasma antigen negative and do not show signs of residual disease. ***DIII***

Aspergillosis

Aspergillus spp. are ubiquitous environmental fungi capable of causing a wide variety of manifestations ranging from allergic aspergillosis to invasive disease (124). The first reported case of *A. fumigatus* pneumonia in a patient with RA was probably that of a 73-year-old woman treated with multiple immunosuppressive agents who possibly acquired the infection during hospital construction (125), and another involved concurrent infection with *A. fumigatus*, TB and herpes simplex (126). Other cases of aspergillus infection (20 associated with infliximab and 10 associated with etanercept) have been reported, but no clinical details were provided (127). TNFIs may increase the risk of developing aspergillosis by inhibiting neutrophil recruitment, and murine models have confirmed increased mortality due to aspergillus in the presence of TNF-α inhibition (127).

The main risk factor for invasive pulmonary aspergillosis is prolonged severe neutropenia.

Invasive pulmonary aspergillosis in RA patients should be treated in accordance with the international guidelines (128)

Questions and statements

What should be done in the case of patients who have invasive pulmonary aspergillosis? *Discontinuing immunosuppressive therapy seems to be mandatory.* ***DIII***

Is re-treatment with biological DMARDs possible?

Re-treatment might be considered after a full course of antifungal therapy and the reversal of neutropenia. ***DIII***

Conclusions

Although infrequent, a PFI occurring in patients with RA is a critical event that requires immediate therapeutic management decisions (Table I, II). The small number of cases reported in studies and the national registers of patients treated with bDMARDS does not allow the extrapolation of data from meta-analyses and limits the possibility of drawing up recommendations to clinical experience and expert opinion (129-131). It is also unclear whether the risk of developing a PFI is different depending on the administered TNFI. Although there is no evidence that the incidence of PFI is increasing despite the extended use of bDMARDs, the prolonged life expectancy of RA patients, the probable future increase in the use of bDMARDs and more complicated therapeutic regimens, and the resulting increase in the number of severe immunodepressed patients (132), make it necessary to pay special attention to the occurrence of PFIs.

Take-home messages

- Pulmonary fungal infections (PFIs) can occur in patients with rheumatoid arthritis (RA) receiving disease-modifying anti-rheumatic drugs (DMARDs).
- *Pneumocystis jirovecii* pneumonia (PJP) has rarely been seen outside Japan.
- Pulmonary cryptococcosis has been diagnosed in only a small number of patients worldwide. Pulmonary coccidioidomycosis has almost only been observed in endemic areas.
- Many aspects of the prophylaxis, diagnosis and treatment of PFIs in RA patients remain to be defined.
- The possibility of resuming biological and non-biological DMARD treatment after the infection has been cured, it has been discussed.

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