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Therapeutic effects of Rheumatoid Arthritis on Aspergillosis development

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ABSTRACT

Aspergillosis is a common fungal infection with systemic characteristics, which is caused by various species of *Aspergillus*. The infection could develop in immunocompromised and immunocompetent patients under specific circumstances. Based on the clinical features and type of invasion, aspergillosis could be classified into four main categories, including invasive pulmonary aspergillosis (IPA), noninvasive aspergilloma, semi-invasive chronic pulmonary aspergillosis, and allergic bronchopulmonary aspergillosis (ABPA). Treatment with immunosuppressive drugs for inflammatory diseases, such as rheumatoid arthritis (RA), increases the infection rate with aspergillosis. RA is an autoimmune disease characterized by several chronic symptoms in the joints, including pain, stiffness, and chronic synovitis. Previous studies have denoted an association between RA and aspergillosis. Inhibitory drugs of tumor necrosis factors and steroids are widely used in the treatment of RA. ABPA and IPA are the most commonly diagnosed diseases in patients with RA. The present study aimed to review the effects of RA and its treatment on the development of aspergillosis.

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Introduction

Rheumatoid arthritis (RA) is a prevalent chronic disease, which may develop due to the interactions of genetic and environmental factors (1, 2). The destructive and inflammatory features of RA are mostly treated using various immunosuppressive drugs (3). However, the debilitating effects of these drugs on the immune function promote various pathogenic organisms (e.g fungi) to cause infections.

Aspergillosis is mainly caused by exposure to Aspergillus spp., which is an opportunistic organism (4-6). Aspergillosis is frequently diagnosed in the immunocompromised patients receiving treatment with immunosuppressive agents or those with other immunological disorders and viral infections (7-9). Aspergillosis may encompass different pulmonary infections, ranging from infections with low severity in immunocompetent patients (e.g. aspergilloma) to the more severe types, such as invasive pulmonary aspergillosis (IPA) (10).

Patients with RA often receive treatment with immunosuppressive agents such as steroids or immunomodulating drugs, especially the inhibitors of recombinant human tumor necrosis factor alpha (TNF-α) (11-15). Recently, five types of TNF-α inhibitors have been applied in the treatment of RA (16-19), which act through neutralizing anti-TNF monoclonal antibodies or as the inhibitors of soluble TNF receptors [20-24]. Furthermore, several types of aspergillosis have been reported to develop in patients with RA, such as

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allergic bronchopulmonary aspergillosis (ABPA) and IPA (11-14). IPA and chronic pulmonary aspergillosis (CPA) have been diagnosed in numerous cases of RA treated with TNF inhibitors, such as adalimumab (ADA) and etanercept (ETN) (11, 14, 25, 26).

The present study aimed to review the role of RA treatment in the development of aspergillosis.

Rheumatoid Arthritis

RA is an autoimmune disease, which mainly occurs in the joints and is characterized by pain, stiffness, and chronic synovitis [1]. The morbidity and mortality of RA could increase with the expansion of the disease to extra-articular sites (20, 27). This condition is clearly observable in CT-scan, which shows the presence of four main patterns of lung diseases associated with RA [28]. RA affects approximately 1% of the population worldwide (29), and 30% of RA cases are caused by genetic factors, while the etiology of the remaining cases is uncertain (30).

The interactions between environmental factors (e.g. smoking habits) and genetic content (e.g., presence of HLA-DR shared epitope [SE] genes) is associated with 21-fold increase in the risk of RA (2). Moreover, the risk for RA increases in case of the positive results of the anti-citrullinated protein antibody test, which is clearly observed between textile dust exposure and HLA-DRB1 SE (31). However, this interaction stimulates a cascade of immune reactions, thereby leading to severe damage in the joints, structural bones, and synovitis, as indicated by pain and disability, along with emotional, social, and economic challenges (29). Therefore, the recognition of such interactions between genetic and environmental factors could contribute to the development of models to predict RA prior to the onset of the symptoms and finding proper strategies for the prevention of the disease (32).

RA is not associated with specific age ranges or gender, and all age groups may be at the risk of the disease (1). RA development could be easily noticed in the primary age groups of men and women (30). Menopause is has been associated with the increasing rate of RA, resulting from the acute decline in the ovarian function in menopausal women (33). In addition, race has been reported to be involved in the development of RA as reported in Caucasian and Korean populations, who have shown variable genetic risk factors for RA development (34). Diagnosis of RA mainly depends on the results of serological tests, starting with IgG-rheumatoid factor (RF), followed by the measurement of matrix metalloproteinase 3 in case of positive RF or anti-cyclic citrullinated peptide antibodies (anti-CCP antibodies) with negative RF (35). According to the literature, RF is detected in approximately 80% of the patients with RA (36). Moreover, several non-specific tests could determine systemic inflammations, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which provide the optimal information on the acute phase of RA (36-37). Synovial fluid analysis may also reveal inflammatory changes and other abnormalities, allowing the diagnostic features in RA patients (36). However, the anti-CCP test is considered to be more specific (92.4%) and sensitive (81%) for RA diagnosis (35) and should be used along with RF to increase the efficiency of RA diagnosis [38, 39]. On the other hand, negative RF results and anti-CCP are expected to be obtained even in the presence of the clinical features of RA as observed in 30-40% of the RA patients with normal ESR and CRP results (40). The infections that often develop in patients with RA are caused by the immunomodulatory effects of RA or immunocompromising effects of the immunosuppressive drugs used for RA treatment (3).

Aspergillosis

Aspergillosis is a general term referring to the diseases caused by *Aspergillus* spp., which are widely distributed in various environments (4-6). *Aspergillus* is mainly found as a saprophytic fungal genus in the environments that are rich in organic materials (4, 7, 8, 41). The most common pathogenic species of this genus is A. fumigatus considering its ability to cause various types of aspergillosis (5, 7, 41). The immune state of the human body is an important factor contributing to the development of aspergillosis. The innate immune system includes pattern recognition receptors, phagocytosis, and production of antimicrobial peptide and is the first defensive line against the entry of *Aspergillus* conidia (10).

Most of the patients with aspergillosis infection have an impaired immune system, which may have resulted from the excessive use of immunosuppressive drugs or the presence of other immunological disorders and viral infections (7-9). As such, the number of the cases with aspergillosis has been gradually on the rise given the association with the availability of facilitating conditions (7). Furthermore, the associated mortality rate has been reported to be higher in most of the severe cases of aspergillosis (8, 42). Aspergillosis may encompass various pulmonary diseases, ranging from low severity in immunocompetent patients (e.g., aspergilloma) to the more destructive types in immunocompromised patients (e.g., IPA) (10).

Aspergillosis could be classified into four main types based on the clinical features and type of

invasion, including IPA, noninvasive aspergilloma, semi-invasive CPA, and ABPA [5, 41].

1. Invasive Pulmonary Aspergillosis (IPA)

IPA is a severe form of aspergillosis infection with high mortality (50%), especially in immunocompromised patients (7, 9, 41, 43); the mortality may reach 100% in patients with allogeneic bone marrow transplant (BMT) (5, 41). The annual estimates of IPA are approximately 2,901-2,912 cases in the United Kingdom (44), and the case fatality rate of IPA has been reported to be 58%, which is considered to be higher (86.7%) in BMT recipients and patients with disseminated and central nervous system aspergillosis (88.1%)(45). A defective immune system is mainly expected in the patients receiving immunosuppressive treatment for cell/solid organ transplantation and malignant diseases, such as neutropenia during chronic granulomatous disease and viral infections (HIV-AIDS and cytomegalovirus) (4, 5, 41). The incidence of IPA has been estimated at 5-25% in patients with acute leukemia, 5-10% following BMT, and 4% in AIDS patients (41). Other diseases could also be associated with IPA development, such as chronic obstructive pulmonary disease (COPD; 1.3-3.9%) (4, 7).

According to the literature, inhalation is the main route of *Aspergillus* conidial entry in almost all IPA cases (9). IPA infection starts from the germination of the escaped conidia into the hyphae, which gives rise to the invasion of the tissues of the lower respiratory tract, thereby causing tissue damage (5). Immune deficiency increased the damage caused by the fungal hyphae and leads to the development of invasive aspergillosis. Although hundreds of conidia are inhaled into the lung every day, IPA is considered to be a rare disease since most of the entering conidia are destroyed by an efficient immune system (5, 7, 43). Depending on organ localization, IPA is clinically classified as acute/chronic pulmonary aspergillosis (common form), tracheobronchitis and obstructive bronchial aspergillosis with some invasion into the mucosal layer, acute invasive rhinosinusitis, and disseminated aspergillosis (41).

The diagnosis of IPA remains challenging to most physicians (41), and the survival of the patients is critically dependent on the early diagnosis of IPA as delayed diagnosis could definitely lead to death (4). Over the years, the increased number of the risk factors for IPA has made clinicians familiar with the possibility to suspect the involvement of any aspergillosis types with other pulmonary diseases, especially in immunocompromised patients (43). In fact, there is no consensus regarding the optimal criteria to improve IPA diagnosis. Therefore, four terms are considered acceptable to explain the diagnostic features of IPA, including highly probable, probable, possible, and suspected (41). However, the increased efficiency of diagnosis requires the establishment a combination of clinical, radiological, and microbiological features (4). Clinical features alone do not suffice to indicate the possible presence of IPA due to the nonspecific features of the disease (41), and the diagnostic rate enhances with the support of positive radiology, microscopic/cultural positive results of histological samples, and detection of *Aspergillus* antigen in the serum (5, 41). The radiological features of IPA often show the presence of the nodules surrounded by a halo of ground-glass attenuation (halo sign) or wedge-shaped consolidation areas (pleura-based) in CT-scan images (46). In addition to histological examination, the bronchoalveolar lavage fluid represents the most proper sample for the diagnosis of IPA with 50% sensitivity and 97% specificity (5).

IPA treatment should be considered an emergency due to the rapid progress of the disease, which often occurs within 1-2 weeks between the disease onset and subsequent mortality (41). The systemic administration of antifungal agents has been reported to yield more successful outcomes, especially in immunocompromised patients (42). Voriconazole is the first-line recommendation for the treatment of IPA rather than amphotericin B (AmB) (4, 9, 42). Various AmB formulas have been shown to reduce the risk of mortality in half to two-thirds of the patients with IPA (45). Furthermore, antifungal combinations could decrease the recovery period and mortality rate (9), while other antifungal agents may significantly prevent IPA development (e.g., posaconazole and isavuconazole) (4, 42). However, the antifungal therapy of IPA should continue for a minimum of 12 weeks or more depending on the clinical response and immunity level of the patients (4).

Obtaining satisfactory treatments to minimize the mortality rate of IPA is not only dependent on antifungal therapy, but it also requires the support of the immune system, treatment of the underlying diseases, and use of surgical management in some cases (5, 45). Therefore, clinicians may initiate treatment without waiting for the diagnostic results in order to reduce the treatment period and overcome the diagnostic difficulty (4, 41). Prophylaxis by antifungal agents has also been associated with the reduction of IPA in most of the patients at the risk of IPA (42).

2. Aspergilloma

Aspergilloma, also known as fungal ball, is a saprophytic form of aspergillosis without invasive features [41, 47]. It mainly develops singly in the lung cavities formed by previous diseases (e.g.,

tuberculosis, sarcoidosis, and bullous lung disorders) or in the sinus cavities due to chronically obstructive paranasal sinuses (7, 10, 41, 46). Approximately 58% of Japanese patients with aspergilloma have a history of tuberculosis (47). However, infection with aspergilloma could develop in both immunocompetent and immunocompromised patients (48). Various species of *Aspergillus* are able to cause aspergilloma. In addition to A. fumigatus, A. flavus has been diagnosed as a causative agent of aspergilloma (49).

Fungal ball, which takes the form of a nodule at the outset of the infection, is mainly composed of a mass of fungal hypha, embedded in an extracellular matrix of protein and separated from the cavity wall by an air space (8, 10, 46, 48). A ball could extend later outside the cavity, thereby causing the obstruction of the airway passage (8, 41, 47). Although patients with aspergilloma are often asymptomatic, hemoptysis has been observed in most of the cases as result of the damage to the blood vessels of the wall of the cavity occupied by the fungi or from the close bronchial artery (41); the hemoptysis may be fatal in some cases (47). The asymptomatic feature of aspergilloma makes the early diagnosis of the infection rather difficult, and most of the cases are misdiagnosed with other pulmonary or allergic diseases in the chest X-ray (41). As such, the radiological features of the thickened wall of the cavity with fungal ball (especially by CT-scan) and serological detection of the fungal antigen in the serum are the most common diagnostic tools for aspergilloma (41, 47, 48). The surgical excision of the fungal ball is considered to be the optimal treatment choice in this regard (8, 47), while antifungal therapy could be an alternative in case of difficulty in performing the operation (47).

3. Chronic Pulmonary Aspergillosis (CPA)

CPA generally refers to several diseases caused by *Aspergillus* spp. in mildly immunocompromised patients or those with preexisting pulmonary diseases (4, 7, 9). The most common diseases covered by the term CPA are aspergilloma, which differs from single aspergilloma due to the presence of many fungal balls, chronic cavitary pulmonary aspergillosis (CCPA), chronic fibrosing pulmonary aspergillosis (CFPA), chronic necrotizing pulmonary aspergillosis (CNPA), and *Aspergillus* nodules (4, 47). CCPA is the most common form of CPA, which may progress to CFPA if untreated, while single aspergilloma and *Aspergillus* nodule are the less prevalent types of CPA (47, 48), often affecting middle-age individuals (5). However, the destructive nature of the slowly progressive inflammation of CCPA (less than 3 months) makes it different with IPA, which is characterized by significant damage to the lung tissues over a short period (5, 48).

The predisposing factors for the development of CPA range from previous tuberculosis infection, non-tuberculous mycobacterial infection, and ABPA to mildly immunocompromised conditions (e.g., diabetes, alcoholism, malnutrition, COPD, chronic liver disease, low-dose corticosteroid therapy or RA) (4, 5, 7, 9, 50). Therefore, CPA development complicates many other respiratory disorders. According to statistics, CPA affects 3,600 patients with a history of tuberculosis or sarcoidosis in the United Kingdom (44). The annual incidence of CPA has been estimated at 27,000-170,000 with 15% mortality (46). In addition, CPA has been reported to affect approximately 240,000 individuals in Europe (48).

The diagnostic expectation regarding the presence of CPA should be considered in patients with mild immunocompromised conditions and those with upper-lobe cavitary or fibrotic pulmonary diseases (50). The presence of several thin/thick wall cavities containing one or more fungal balls is considered to be a primary indicator of the presence of CCPA (48). The confirmation of the disease diagnosis could be attained by performing several serological, immunological, and microbiological tests to detect *Aspergillus* infections and determine the systemic symptoms based on radiological tests over a minimum of three months of observation (4, 5, 48, 50). Moreover, an immunological precipitin test for the detection of *Aspergillus* antibodies is elevated in more than 90% of the patients (4, 48).

Prolonged and relapsing symptoms of cough, weight loss, dyspnea, hemoptysis, and bronchial/pulmonary hemorrhage may also be the indications of CPA (51). CNPA is a developed form of aspergilloma, which could be diagnosed depending on the detection of several features in radiological images (progressive shadow, a fungal ball with a thick wall cavity, endobronchial mass, obstructive pneumonitis, and hilar mass), as well as symptoms such as cough, sputum, hemoptysis/fever, proven *Aspergillus* infection, and positive inflammatory reaction (46, 47, 52).

Long-term therapy with the antifungal azole group is strongly recommended for the treatment of CPA (4, 42, 48, 51) since it improves the respiratory symptoms and arrests hemoptysis through the reduction of the disease progression (48). In this regard, oral voriconazole and itraconazole are the preferred azole groups for the prolonged treatment of CPA (42). Moreover, AmB and echinocandins could be used as the alternatives to azole agents in case of resistance to azole, azole intolerance or treatment failure (42, 51). Surgical

options may also be beneficial in the cases with localized diseases (42).

4. Allergic Bronchopulmonary Aspergillosis (ABPA)

ABPA is a hypersensitivity reaction to the *Aspergillus* antigen (especially A. fumigatus), causing pulmonary diseases in patients with other immune disorders, such as atopic asthma and cystic fibrosis (4, 7, 41, 43). ABPA mostly affects immunocompetent patients (41). Fungal antigens may originate from long-term exposure to fungal elements or hyphal colonization in the lungs (9), as observed in approximately 1-2% of asthmatic patients and 7-35% of those with cystic fibrosis (41). Other estimates have indicated the presence of ABPA in 178,000 asthmatic patients, as well as 873 adults and 278 children with cystic fibrosis (44). The development of ABPA in asthmatic patients often leads to more damages to the respiratory tract, such as obstruction due to the accumulation of mucous in the distal airway, eosinophilic pneumonia, bronchiectasis, and severe fibrosis (5).

The complications and nonspecific features of ABPA render the diagnosis very challenging based on only one test (4). Therefore, the International Society for Human and Animal Mycology has proposed several diagnostic criteria for ABPA, including the presence of predisposing diseases (e.g., asthma and cystic fibrosis), peripheral blood eosinophilia count of more than 1,000 mm-3, total *Aspergillus*-specific IgE level of more than 1000 mg/ml, positive skin test to *Aspergillus* antigens, central bronchiectasis, and history of pulmonary infiltrates (4, 41). On the other hand, the examination of the CT-scan image of patients with ABPA has indicated the presence of bronchiectasis and mucoid impaction in the bronchi of the upper lobes (46).

The successful treatment of ABPA should be focused on minimizing pulmonary damage through the inflammatory reaction caused by exposure to *Aspergillus* antigens (5, 8). In addition, short-term treatment with steroids and long-term treatment with antifungal agents have proven effective in ABPA treatment (4-5, 8). Steroids are commonly used in the cases with exacerbated ABPA (4); for instance, itraconazole therapy for several months is often preferred for the treatment of ABPA (8).

RA and Aspergillosis

Evidence suggests the unusual association between fungal infections and the increased severity of some systemic autoimmune diseases, such as RA. Such association has been observed between aspergillosis infection and development of RA. A survey of RA patients with aspergillosis in three university hospitals in France was conducted during 1999-2007, which demonstrated that 10 out of 550 patients had both RA and aspergillosis infection (53).

In patients with RA, chronic inflammatory reaction is often treated with a group of immunosuppressive drugs (3), which weakens the immune function, thereby increasing the susceptibility of the human body to various infections, such as fungal infections. The most common immunosuppressive drugs used for the treatment of RA are steroids or immunomodulating agents, especially recombinant human TNFα inhibitors (11-15). These drugs have been reported to increase the risk of various aspergillosis infections.

ABPA is a common allergic aspergillosis infection, which has been reported to develop in RA patients. The current body of data suggests that the disease is diagnosed in three cases of elderly women with RA; the first case of ABPA was diagnosed in a 77-year-old woman experiencing RA for a minimum of 15 years, who received treatment with methotrexate (MTX) and adalimumab (ADA) for the past three years. The serological tests of the patient indicated the presence of aspergillosis, including high levels of eosinophilia, *Aspergillus*-specific IgE, and *A. fumigatus* serum precipitins, while fungal elements were also detected in plugs of the patient by pathological examination (11). The second case was an elderly woman with bronchocentric granulomatosis associated with RA, who received treatment with abatacept for 12 months. In addition, A. fumigatus was diagnosed inside the suppurative cavitation of the right upper lobe of the lung (12). The third case was a woman with stage III and class II RA, who developed ABPA after treatment with ETN or tocilizumab. The patient had high levels of eosinophilia and *Aspergillus*-specific IgE, while *Aspergillus* spp. was detected in the plugs of the patient by culturing (13). Several studies have also indicated the diagnosis of aspergilloma in the patients with RA receiving treatment with steroids (54, 55) or TNFα inhibitors (53).

IPA is the more hazardous form of *Aspergillus* infection, which could cause systemic aspergillosis and has been associated with several cases of RA resulting from drug therapy. One of the reported cases in this regard was a woman with RA and tuberculosis infection, who was diagnosed with IPA after treatment with infliximab (15), while another case of RA was reported to develop IPA infection after treatment with low-dose MTX (5-7.5 mg/week) for eight years (56).

ADA is a TNFα inhibitor, which has been shown to cause fatal IPA infection in a woman with RA (14). A very rare type of aspergillosis represented by CPA has also been reported to occur in patients

with RA. For instance, a man with RA was diagnosed with CPA in the form of slowly progressing chronic multiple nodular pulmonary aspergillosis (25). Another case of CPA resulting from treatment with ETN has been reported in an elderly woman with a 10-year history of severe RA (26). *Aspergillus* arthritis (AA) is a new term describing the association of invasive aspergillosis with inflammatory reaction in one or more joints. Fungal infections have reported to be involved in the site of arthritis (57-60). However, data on AA are not complete in terms of the epidemiology, laboratory features, clinical features, and treatment. Approximately 31 cases of AA were recorded during 1967-2015 based on a review of the English literature, with the disease affecting 27 adults, four pediatric patients, and one infant aged less than 12 months (57). A. fumigatus is considered to be the major causative agent of AA (49-60), which has been isolated from the synovial fluid and tissue sample cultures of an elderly man with arthritis and patellar osteomyelitis of the left knee (58). Furthermore, A. fumigatus accounts for 77% of the 31 cases with AA, followed by A. flavus and A. niger (57). Septic arthritis caused by A. fumigatus has been observed in several patients with diabetes mellitus or those receiving local injection with corticosteroids (59, 60).

TNF Inhibitors in the Treatment of RA

TNFs are highly effective cytokines in various activities of the innate and adaptive immune system (61, 21), which have been entitled based on the in-vitro detection of their ability to destroy tumor cells and cause necrosis (16). TNFs could be found in the two forms of TNFα and TNFβ (lymphotoxin), which are similar in their three-dimensional structures and differ in their primary structures (16, 20). These factors have many biological effects on human cells, such as cell survival, proliferation, differentiation, and death (21). The biological activities of TNFs are often performed via various signal pathways, such as the nuclear factor κB (anti-apoptotic action) and c-Jun N-terminal kinase (contributing to cell death) (21).

TNFα is an important type of TNFs, which is involved in various immune activities in the human body, such as the stimulation of monocyte/macrophage differentiation, B cell proliferation, and inflammation against microbial infections (61). Increased platelet activation and adhesion leads to blood vessel occlusion and may be associated with the antimicrobial action of TNFα (22). TNFα is mainly synthesized by immune cells such as macrophages, astroglia, microglia, Langerhans cells, and Kupffer cells (17, 62).

Proinflammatory activity is an important action of TNFs, which leads to various inflammatory diseases, such as RA, as well as local joint damage and systemic bone loss as clearly proven by several experimental studies (63). Moreover, TNFα has inflammatory actions in the development of RA as its levels have been observed to be significantly higher in patients with RA (17, 22, 23). The overexpression of TNFα leads to the regulation of the inflammatory reactions that may cause damage to the cartilage, bones, and bowel mucosa (23, 64). The initiation of the inflammatory reaction mediated by TNFα often results from the stimulation of inflammatory cells and antibodies or complements following the local activities of this cytokine in the vascular vessels, which is associated with the increased expression of class II major histocompatibility molecules (22). However, all the biological activities of TNFα could be regulated through two transmembrane receptors, including TNFR1 and TNFR2 (17).

RA is a chronic inflammatory disease, which commonly leads to joint destruction, followed by increased disability, poor quality of life, and even mortality in some cases (20, 27). The control of joint damage is considered to be the primary goal of RA treatment (27, 62, 65). Such damage often results from an inflammatory reaction regulated by TNFα, which plays a pivotal role in RA development (17, 24, 63). Therefore, the blocking of TNFα activity results in the more successful treatment of RA compared to the blocking of other cytokines, such as interleukin 1 (17-19, 23). In general, the most commonly used drugs in the treatment of RA are steroids, non-steroidal anti-inflammatory drug, T-cell activation inhibitors, disease-modifying anti-rheumatic drugs (DMARDs), TNFα inhibitors, interleukin 6 inhibitors, B-cell depletion agents, and Janus kinase inhibitors (65). Moreover, anti-TNRα drugs are most commonly used in RA treatment (16-19). The inhibition of TNR as an RA treatment method could be performed using anti-TNF neutralizing monoclonal antibodies, soluble TNF receptors or TNF autovaccination (20-24). These biological compounds have recently been synthesized from protein molecules, genes, and antibodies of living organisms using genetic engineering methods (18).

TNFα inhibitors were first used in the animal models of sepsis in 1985 [27]. TNF inhibitors were also licensed for the treatment of inflammatory diseases in 1998 and approved by the FDA for use in the treatment of various immune diseases, such as RA, inflammatory bowel disease, ankylosing spondylitis, juvenile arthritis, psoriasis, and psoriatic arthritis (16, 17). Inflix¬imab (IFX) and etanercept (ETN) were the first drugs to receive an FDA approval [18, 20]. According to the literature, anti-TNFα drugs could reduce joint damage,

bone mineral density, and the clinical symptoms of RA more effectively compared to MTX (62-64). Furthermore, they serve as alternative drugs in cases of failure or the intolerable adverse effects of conventional DMARDs (61, 64). Recently, approximately one million individuals have received treatment with anti-TNF drugs worldwide after the widespread availability of these agents on the pharmaceutical market (20).

Five TNF inhibitors are currently available for the treatment of RA, including three TNF-specific monoclonal antibodies (IFX, ADA, and golimumab [GOL]), one soluble TNF receptor-Fc fusion protein (ETN), and one TNF-specific Fab fragment bound to polyethylene glycol (certolizumab pegol [CZP]) (16, 19, 61, 62, 64, 66). CTP-13 is a new biosimilar to IFX, which has been approved by the European Medicines Agency (EMA) for RA treatment (63). Three monoclonals and ETN contain the Fc fragment of the human IgG1, which enables them to easily attach to the Fc receptors on the immune cells, while such quality is not observed in CZP (66). Nonetheless, all TNF inhibitors are similar in terms of their binding ability to TNFα, while they differ in their molecular structures, mode of action, and administration regimens (27).

IFX (Remicade®-Centocor/Schering-Plough) is a chimeric IgG1 protein consisting of 25% mouse and 75% human monoclonal antibody with the molecular weight of 149 kDa (16, 20, 23, 24, 64). IFX has an affinity to only affect soluble and membrane-bound TNFα through inhibiting the binding of this cytokine to the TNF-RI and TNF-RII receptors (16, 20, 23, 27). This TNF inhibitor is also used the treatment of RA, ankylosing spondylitis and Crohn's disease (16, 64).

IFX is often administered via intravenous infusion every eight weeks at the dosage of 3-6 mg/kg and could be used in single doses as well (1-20 mg/kg), which are effective for one month (16, 23, 24, 27, 62). The half-life of IFX is within the range of 9-12 days (62, 66). IFX was approved by the FDA for the treatment of RA in 1999 (18). The common adverse effects of IFX include upper respiratory tract infection, headaches, nausea, sinusitis, rash, and cough (62, 67). In addition, infusion reactions have been observed during treatment with IFX due to immunogenic mouse content in the structure (62).

ADA (Humira®, AbbVie Inc., North Chicago, IL, USA) is another monoclonal antibody of recombinant IgG1, which is purely composed of a human peptide with the molecular weight of 148 kDa (16, 20, 62, 64). ADA has high affinity to bind to soluble and membrane-bound TNFα (16, 27). As a difference with IFX, the absence of non-human compounds makes ADA less immunogenic with slight stimulation to form the antibodies that are against this compound (16, 64). Furthermore, ADA is often administered subcutaneously at the doses of 25-40 milligrams twice per week and could be used in the form of monotherapy or in combination with other DMARDs, such as MTX (16, 23, 27, 62, 64). The half-life of ADA is often higher than IFX (range: 10-20 days) (62, 66). The FDA and EMA (2003) approved ADA for use in the treatment of non-infectious inflammatory diseases (e.g. RA), ulcerative colitis, Crohn's disease, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, and juvenile idiopathic arthritis (16, 20). In addition, ADA was approved later by the FDA (2016) for the treatment of posterior and panuveitis in adults and older children (aged more than two years) [16]. ADA is considered to be a safer therapeutic option with fewer adverse effects than other TNF inhibitors (16, 62). The rare side-effects of ADA may include infections, neuropathic effects, and malignancies in the lymphoid system (23).

GOL (Simponi® and Simponi Aria®, Janssen Biotech, Inc., Horsham, PA, USA) is another human monoclonal antibody consisting of a chimeric immunoglobulin G (G1κ mAb) (16, 20, 62), which prevents the binding of transmembrane and soluble TNFα with its receptors (16, 20, 27, 62). In general, 50 milligrams of GOL is subcutaneously administrated every four weeks, which could increase to 100 milligrams in the absence of response after the administration of four consecutive doses (27). GOL could also be applied via intravenous infusion at various doses, starting at two milligrams per kilogram in weeks zero and four, remaining steady every eight weeks (16). In 2009, GOL was approved by the FDA for the treatment of RA (16, 20). Similar to ADA, the human component of GOL and absence of the mouse immunogenic part result in the long half-life of this drug since no antibodies are produced against this compound (16). The side-effects of GOL do not differ significantly with those of other TNF inhibitors, while GOL does not give rise to lupus-like syndrome (16).

ETN (Enbrel®, Amgen Wyeth, Immunex Corporation, Thousand Oaks, CA, USA) is a genetically engineered fusion protein (150 kDa), with the composite of a dimeric soluble TNFα receptor II (p75), which is linked to the Fc portion of the human IgG1 (20, 23, 24, 27, 62). In contrast with other TNF inhibitors, ETN has the ability to neutralize both TNFα and TNFβ (16). The binding of ETN to two types of TNF is mainly associated with its dimeric structure, which makes it approximately 1,000 times more efficient to accomplish such binding (23). In the treatment of RA, ETN is often administered subcutaneously at the dose of 50 milligrams

in one week or 25 milligrams twice per week with a low half-life (3 5.5 days) (16, 23, 27, 62, 64, 66). ETN was the first TNF inhibitor to be approved by the FDA in 1998 for the treatment of RA, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis (16, 18). ETN could be used alone or in combination with MTX in the treatment of RA (62). A sustained effect has been observed in long-term ETN treatment (23). Some of the side-effects of ETN include infusion reaction and mild infection in the upper respiratory tract (24).

CZP (Cimzia®, UCB, Inc., Smyrna, GA, USA) is a recombinant Fab fragment of the human TNFα coupled to PEG (16, 20, 27). The coupling of the humanized Fab fragment with PEG rather than the Fc region of IgG reduces the antigenicity of CZP, while increasing its half-life (two weeks) (16, 27). CZP has the affinity to bind to TNFα (23). In 2009, CZP was approved by the EMA for the treatment of RA (20). It is generally administered subcutaneously at the dose of 400 milligrams every two weeks for six weeks, followed by 200 milligrams every two weeks or 400 milligrams monthly (16, 23, 27).

The efficiency of TNF inhibitors in the treatment of RA could enhance in combination with the other drugs that are commonly used for the same purpose (68). Most of these combinations are with MTX or other DMARDs in order to reduce RA severity by slowing-down the process of joint destruction (20, 62, 64, 68). In addition, the combination of ADA, CZP, IFX or GOL with MTX has been reported to relieve the symptoms of RA (16, 23, 27, 62, 64).

Adverse effects of TNF inhibitors

Inhibition of TNF affects the efficiency of various defensive activities of the immune system and also the pathways of some physiological functions. These activities can lead at the end to many adverse effects that are noticed after use of TNF inhibitors and may decrease the suitability of treatment with the drugs of this group. Thus, monitoring of clinical features while treating patients with TNF inhibitors is becoming necessary to avoid harmful effects of drugs (16, 18). In addition to monitoring, the risks of using these drugs can be limited by appropriate screening for infection or other diseases, careful choice of the patient, and building better connections between primary care physicians and subspecialists (18). Usage of TNF inhibitor is usually different from one patient to another, depending on characters such as patient's weight, drug clearance and metabolism (22). The most adverse effects and disadvantages of TNF inhibitor treatment can be summarized as follows (16, 18, 20, 27, 62, 64,66, 69):

1. Infusion reaction: Injection of TNF inhibitor as infusion drugs can lead to many hypersensitivity reactions that characterizing by eczema like eruptions, pain, swelling and itching at the site of injection and also symptoms of fever, vomiting and arthralgia.
2. Infection: Blocking of the immune function of TNF, especially TNF-α, can encourage several pathogenic organisms to cause infections such as opportunistic fungi (histoplasmosis and coccidioidomycosis) and also can activate latent infections as with tuberculosis and hepatitis virus.
3- Malignancies: TNF inhibitors have been found potentially associated with the development of some malignant diseases such as lymphoma and melanoma in children and young adults.
4. Cardiovascular effects: Heart can be affected by treatment with TNF inhibitors after observing the formation of atherosclerosis, hypertrophy, heart failure, and promotion of plaque rupture
5. Neuropathies: Demyelinating disease and vasculitic neuropathies are found associated with treatment with TNF inhibitors.
6. Autoimmune diseases: An inducing of autoimmune diseases could be predicted through the stimulation of TNF inhibitors to form auto-antibodies such as anti-DNA, antinuclear, and anti-cardiolipin antibodies. CZP is most suggested drug associated with autoimmune reaction.
7. Lack of response: In some cases of patients with RA (30%), there was no response to the treatment with TNF inhibitors as indicated by test results of rheumatoid factor and anti-cyclic citrullinated protein antibodies.
8. Expensive cost: TNF inhibitors are considered expensive drugs which the cost may exceed $18 000 per year.

Conclusion

Rheumatoid arthritis is a common autoimmunologic disease with an inflammatory nature in the joints. Decrease the inflammatory reaction in patients with RA is usually achieved by many available immunosuppressive drugs, especially inhibitors of recombinant human tumor necrosis factor (TNFs). Five types of TNF inhibitors are widely used in the treatment of RA now days. This debilitating effect of TNF inhibitors will increase the susceptibility of patients to infect with various fungal infections. Aspergillosis caused by *Aspergillus* spp. is one of assumption infection in RA due to treatment with any of TNF inhibitor. The most predictable type of aspergillosis in RA patient is an invasive pulmonary aspergillosis (IPA) which is more frequent in immunocompromised patients.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Birch JT Jr, Bhattacharya S. Emerging trends in diagnosis and treatment of rheumatoid arthritis. Prim Care. 2010;37:779-792.
2. Klareskog L, Stolt P, Lundberg K, et al. A new model for an etiology of rheumatoid arthritis. Smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum. 2006;54:38-46.
3. Doran MF. Frequency of infection in patients with rheumatoid arthritis compared with controls: A population-based study. Arthritis Rheum. 2002;46:2287-2293.
4. Bazaz R, Denning DW. Aspergillosis: causes, types and treatment. The Pharmaceutical J. 2019:303.
5. Pasqualotto AC. Aspergillosis: From diagnosis to prevention. Springer, New York. 2010.
6. Barnes PD, Marr KA. Aspergillosis: Spectrum of disease, diagnosis and treatment. Infect Dis Clin North Am. 2006;20:545-561.
7. Kousha M, Tadi R, Soubani AO. Pulmonary aspergillosis: a clinical review. European Respiratory Review 2011 20: 156-174.
8. Kulkarni HS. Aspergillosis, fungal disease series #4. Patient information series. Am J Respir Crit Care Med. 2012;186:1-2.
9. Sherif R, Segal BH. Pulmonary aspergillosis: clinical presentation, diagnostic tests, management and complications. Curr Opin Pulm Med. 2010;16:242-250.
10. Chotirmall SH, AI-Alawi M, Mirkovic B, et al. *Aspergillus*-associated airway disease, inflammation, and the innate immune response. Biomed Res Int. 2013;2013.
11. Kawasaki T, Kamiya M, Nakagawa A, et al. Allergic bronchopulmonary aspergillosis in a patient with rheumatoid arthritis under adalimumab therapy: a case report. Nihon Rinsho Meneki Gakkai Kaishi. 2016;39:84-89.
12. 1Neff K, Stack J, Harney S, et al. The use of abatacept in debilitating cavitating lung disease associated with rheumatoid arthritis, bronchocentric granulomatosis and aspergillosis. Thorax. 2010;65:545-546.
13. Honda H, Kida H, Yoshida M, et al. Recurrent allergic bronchopulmonary aspergillosis in a patient with rheumatoid arthritis treated with etanercept and tocilizumab. Mod Rheumatol. 2011;21:660-664.
14. Kim JH, Bae JK, Jun JW, et al. A case of invasive pulmonary aspergillosis in a patient with rheumatoid arthritis treated with adalimumab. J Rheum Dis. 2011, 18: 212-215.
15. Shaz D, de Rosa FG, Campagna A, et al. Invasive pulmonary aspergillosis in a patient with rheumatoid arthritis recently treated with infliximab: Emphasis on prophylaxis. 40th Annual Meeting of the Infectious Diseases Society of America. 2002. https://www.aspergillus.org.uk/content/invasive-pulmonary-aspergillosis-patient-rheumatoid-arthritis-recently-treated-infliximab.
16. Chen JL, Lobo-Chan A, Chan RV, et al. Tumor necrosis factor-alpha inhibitory therapy for non-infectious autoimmune uveitis. IntechOpen. 2019, 1-19.
17. Parameswaran N, Patial S. Tumor necrosis factor-α signaling in macrophages. Crit Rev Eukaryot Gene Expr. 2010;20:87-103.
18. Hadam J, Aoun E, Clarke K, et al. Managing risks of TNF inhibitors: An update for the internist. Cleve Clin J Med. 2014;81:115-127.
19. Davignon J, Rauwel B, Degboé Y, et al. Modulation of T-cell responses by anti-tumor necrosis factor treatments in rheumatoid arthritis: a review. Cleve Clin J Med. 2014;81:115-127.
20. Barbosa ML, Fumian MM, de Miranda AL, et al. Therapeutic approaches for tumor necrosis factor inhibition. Brazillian J Pharm Sci. 2011, 47:427-446.
21. Wang X, Lin Y. Tumor necrosis factor and cancer, buddies or foes?. Acta Pharmacol Sin. 2008; 29: 1275–1288.
22. ODell JR. TNF-α inhibition: The need for a tumor necrosis factor thermostat. Mayo Clin Proc. 2001;76:573-575.
23. Vasanthi P, Nalini G, Rajasekhar G. Role of tumor necrosis factor-alpha in rheumatoid arthritis: a review. APLAR Journal of Rheumatology 2007; 10: 270–274.
24. Fox DA. Cytokine blockade as a new strategy to treat rheumatoid arthritis: inhibition of tumor necrosis factor. Archives of internal medicine. 2000;160:437-44.
25. Ito Y, Tanigawa M, Takemura T, et al. Chronic nodular pulmonary aspergillosis in a patient with rheumatoid arthritis. Intern Med. 2019; 58: 979–984.
26. Lassoued L, Billey T, Sire S, et al. Pulmonary aspergillosis in a patient with rheumatoid arthritis treated with etanercept. Clin Exp Rheumatol. 2004, 22:267-268.
27. Köhler BM, Günther J, Kaudewitz D, et al. Current therapeutic options in the treatment of rheumatoid arthritis. J Clin Med. 2019;8.
28. Tanaka N, Kim JS, Newell JD, et al. Rheumatoid arthritis-related lung diseases: CT findings. Radiology. 2004;232:81-91.
29. Gibofsky A. Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. Am J Manag Care. 2012;18:S295-302.
30. Alarcón GS. Epidemiology of rheumatoid arthritis. Rheum Dis Clin North Am. 1995;21:589-604.
31. 31- Too CL, Muhamad NA, Ilar A, et al. Occupational exposure to textile dust increases the risk of rheumatoid arthritis: results from a Malaysian population-based case-control study. Ann Rheum Dis. 2016;75:997-1002.
32. Deane KD, Norris JM, Holers VM. Preclinicall rheumatoid arthritis: identification, evaluation, and future directions for investigation. Rheum Dis Clin North Am. 2010;36:213-241.
33. Alpizar-Rodriguez D, Mueller RB, Möller B, et al. Female hormonal factors and the development of anti-citrullinated protein antibodies in women at risk of rheumatoid arthritis. Rheumatology. 2017, 56:1579-1585.
34. Lee H, Korman BD, Le JM, et al. Lack of association of Caucasian rheumatoid arthritis susceptibility loci in a Korean population. Arthritis Rheum. 2009; 60: 364–371.
35. Kumagai S, Nishimura K, Hayashi N. Topics on immunological tests for rheumatoid arthritis. Rinsho Byori. 2004;52:836-343.
36. Mackenzie AH. Differential diagnosis of rheumatoid arthritis. Am J Med. 1988 14;85:2-11.
37. Grassi W, De Angelis R, Lamanna G, et al. The clinical features of rheumatoid arthritis. Eur J Radiol. 1998;27 Suppl 1:S18-24.
38. van Boekel MA, Vossenaar ER, van den Hoogen FH, et al. Autoantibody systems in rheumatoid arthritis: specificity, sensitivity and diagnostic value. Arthritis Res. 2002;4:87-93.
39. Afzal N, Karim S, Mahmud TE, et al. Evaluation of anti-CCP antibody for diagnosis of rheumatoid arthritis. Clin Lab. 2011;57:895-899
40. Pincus T, Sokka T. Laboratory tests to assess patients with rheumatoid arthritis: advantages and limitations. Rheum Dis Clin North Am. 2009;35:731-734.
41. Latgé J. *Aspergillus fumigatus* and aspergillosis. J Immunol Methods. 2008;335:41-45.
42. 42- Jenks JD, Hoenigl M. Treatment of aspergillosis. J Fungi (Basel). 2018 19;4
43. 4Soubani AO, Chandrasekar PH. The clinical spectrum of pulmonary aspergillosis. Chest. 2002;121:1988-1999.
44. Pegorie M, Denning DW, Welfare W. Estimating the burden of invasive and serious fungal disease in the United Kingdom. J Infect. 2017;74:60-71.
45. Lin S, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: Systematic review of the literature. Clin Infect Dis. 2001;32:358-266.
46. 46- Franquet T, Müller NL, Giménez A, et al. Spectrum of pulmonary aspergillosis: Histologic, Radiographics. 2001;21:825-837.
47. Kohno S, Kobayashi T, Kakeya H, et al. Pulmonary aspergilloma, diagnosis and treatment. Kekkaku. 2003;78:757-763.
48. Denning DW, Cadranel J, Beigelman-Aubry C, et al. Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management. Eur Respir J. 2016;47:45-

68.
49. Pasqualotto AC, Denning DW. An aspergilloma caused by *Aspergillus* flavus. Med Mycol. 2008;46:275-278.
50. Smith NL, Denning DW. Underlying conditions in chronic pulmonary aspergillosis including simple aspergilloma. Eur Respir J. 2011;37:865-872.
51. Schweer KE, Bangard C, Hekmat K, et al. Chronic pulmonary aspergillosis. Mycoses. 2014;57:257-270.
52. Sugino K, Hasegawa C, Sano Get al. Pathophysiological study of chronic necrotizing pulmonary aspergillosis. Jpn J Infect Dis. 2008;61:450-453.
53. Leboime A, Berthelot J, Allanore Y, et al. Sinus aspergilloma in rheumatoid arthritis before or during tumor necrosis factor-alpha antagonist therapy. Athritis Res Therapy. 2009;11: R164.
54. Singh CH, Khanna V, Arora MS. Pulmonary aspergilloma in rheumatoid arthritis. Med J Armed Forces India. 2003;59:254-256.
55. McConnochie K, OSullivan M, Khalil JF, et al. *Aspergillus* colonization of pulmonary rheumatoid nodule. Respiratory Med. 1989, 83:157-160.
56. OReilly S, Hartley P, Jeffers M, et al. Invasive pulmonary aspergillosis associated with low dose methotrexate therapy for rheumatoid arthritis: a case report of treatment with itraconazole. Tuber Lung Dis. 1994;75:153-155.
57. 57- Gamaletsou MN, Rammaert B, Bueno MA, et al. *Aspergillus* arthritis: analysis of clinical manifestations, diagnosis, and treatment of 31 reported cases. Med Mycol. 2017;55:246-254.
58. Bodur H, Ozoran K, Colpan A, et al. Arthritis and osteomyelitis due to *Aspergillus fumigatus*: A 17 years old boy with chronic granulomatous disease. Ann Clin Microbiol Antimicrobials. 2003; 2:2.
59. Dal T, Tekin A, Deveci Ö, et al. Septic arthritis caused by *Aspergillus fumigatus* in an immunosuppressive patient: A case report and review of the literature. J Microbiol Infectious Dis. 2012; 2:29-32.
60. Sohail MR, Smilack JD. *Aspergillus fumigatus* septic arthritis complicating intra-articular corticosteroid injection. Mayo Clin Proc. 2004;79:578-579.
61. Menegatti S, Bianchi E, Rogge L. Anti-TNF therapy in spondyloarthritis and related diseases, impact on the immune system and prediction of treatment responses. Front Immunol. 2019;10:382.
62. Ma X, Xu S. TNF inhibitor therapy for rheumatoid arthritis. Biomed Rep. 2013; 1: 177–184.
63. Manara M, Sinigaglia L. Bone and TNF in rheumatoid arthritis: clinical implications. RMD Open. 2015;1(Suppl 1):e000065.
64. Nash PT, Florin TH. Tumor necrosis factor inhibitors. Med J Aust. 2005;183:205-208.
65. Farrugia M, Baron B. The role of TNF-α in rheumatoid arthritis: a focus on regulatory T cells. J Clin Transl Res. 2016;2:84-90.
66. Mewar D, Wilson A. Treatment of rheumatoid arthritis with tumour necrosis factor inhibitors. Br J Pharmacol. 2011;162:785-791.
67. Papadopoulos CG, Gartzonikas lJ, Pappa TK, et al. Voulgari PV, Drosos AA. Eight-year survival study of first-line tumour necrosis factor α inhibitors in rheumatoid arthritis: real-world data from a university centre registry. Rheumatol Advan Practice. 2019, 0:1-11.
68. Yazici Y, Yazici H. Tumor necrosis factor alpha inhibitors, methotrexate or both? An inquiry into the formal evidence for when they are to be used in rheumatoid arthritis. Clin Exp Rheumatol. 2008;26:449-52.
69. Papagoras C, Voulgari PV, Drosos AA. Strategies after the failure of the first anti-tumor necrosis factor α agent in rheumatoid arthritis. Autoimmunity Rev. 2010, 9:574-582.