Review

Safety profile of anakinra in the management of rheumatologic, metabolic and autoinflammatory disorders

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ABSTRACT

Anakinra is a biologic response modifier that competitively antagonises the biologic effects of interleukin-1, the ancestor pleiotropic proinflammatory cytokine produced by numerous cell types, found in excess in the serum, synovial fluid and any involved tissues of patients with many inflammatory diseases. The magnitude of the risk of different infections, including Mycobacterium tuberculosis *(Mtb) infection, associated with the large use of anakinra in many rheumatologic, metabolic or autoinflammatory disorders is still unknown. In addition, it is unclear whether this effect is modified by the concomitant use of antirheumatic drugs and corticosteroids. The rates of development of Mtb disease in patients treated with anakinra due to rheumatoid arthritis, systemic autoinflammatory diseases, Schnitzler's syndrome, Behçet's disease, adult-onset Still disease, systemic juvenile idiopathic arthritis, gout and diabetes mellitus have been usually very low. However, clinicians must carefully weigh the benefits of biological drugs against their risks, particularly in patients prone to infections. Additional data are needed to understand whether this risk of Mtb infection and reactivation are representative of a class effect related to biologics or whether anakinra bears specifically an intrinsic lower risk in comparison with other biologic drugs.*

Introduction

The treatment of rheumatologic, metabolic, and also autoinflammatory disorders has been revolutionised by the introduction of biologic drugs, designed to inhibit specific components of the immune system that play pivotal roles in fueling inflammation, but this new therapeutic era is also associated with risk of serious or opportunistic infections, such as tuberculosis. In particular, *Mycobacterium tuberculosis* (Mtb) infection is a global health concern, estimated to affect one third of the world's population. Nevertheless, only few subjects (about 5-10%) develop Mtb-related disease, suggesting that the host immune system is able to prevent an overt full-blown tuberculosis (1). In this regard, an adequate interaction between innate and adaptive immune system, including T cells and macrophages, orchestrated by a complex network of several proinflammatory mediators, including tumour necrosis factor (TNF)-α and interleukin (IL)-1, is usually efficient in maintaining an immunological homeostasis against mycobacteria (2). TNF-α is a crucial cytokine involved in the enrollment of different inflammatory cells to form granulomas, allowing the development of a localised infection known as "latent tuberculosis". In addition, TNF-α promotes the recruitment of circulating antigen-specific T lymphocytes as well as monocytes to the site of Mtb infection, and maturation of monocytes to dendritic cells and/or macrophages. Moreover, TNF-α triggers autophagy mechanisms of infected cells via activated macrophages and apoptosis by the activation of cytotoxic T cells, entailing the formation of a tubercular granuloma that prevents a further spread of Mtb infection (3). Several studies on animal models have showed that also IL-1 pathway is essential for controlling acute Mtb infection. Indeed, IL-1 is widely produced at the site of infection during tuberculosis, as revealed by IL-1β expression in granulomas of lungs from patients with tuberculosis. In addition, an imbalance of the IL-1β/IL-1 receptor antagonist, in favour of the first, has been found in patients with active pulmonary tuberculosis, suggest-

ing that IL-1 plays a relevant role in the host defense against tuberculosis (4). Interestingly, genetic studies carried out on the IL-1 gene cluster have also displayed how some polymorphisms may influence the course of Mtb infection in humans (5). Since the employment of anti-TNF-α agents in severe inflammatory diseases has been associated with the reactivation of latent tuberculosis, the inhibition of IL-1 through the recombinant non-glycosylated homolog of the human IL-1 receptor antagonist anakinra (ANK) would represent a safer therapeutic choice than TNF-α inhibitors in many disorders where its use is suitable and when it can replace the anti-TNF agents with comparable efficacy, mostly for patients living in those geographical areas where tuberculosis represents a major international public health problem (6).

Rheumatoid arthritis

Anti-TNF-α agents have proven to be an effective therapeutic choice for patients with rheumatoid arthritis (RA) unresponding to conventional disease-modifying anti-rheumatic drugs, albeit it has long been recognised that they increase the risk of tuberculosis reactivation (7). On the contrary, the anti-IL-1 agent ANK has been used in a considerable number of patients with RA without showing cases of tuberculosis. An extension phase of a randomised double-blind placebo-controlled trial has assessed the long-term safety of ANK on 472 patients with active RA (after 76 weeks of total exposure): no cases of tuberculosis occurred, suggesting that ANK might be considered a safe therapeutic option for managing patients with RA (8). Convincing evidence about the safety of ANK and risk of Mtb infection is also derived from a placebo-controlled double-blind trial on a wide sample of RA patients with coexisting comorbidities, aiming to analyse the overall safety profile of daily ANK administration: 1414 patients were randomly assigned to receive either ANK (100 mg/day) or placebo treatment for 6 months; patients with comorbid conditions, considered to be at high risk for the occurrence of treatment-related adverse events, demonstrated a moderate increase in the incidence of serious infections when compared with patients receiving placebo (2.1% *vs*. 0.4%) (9). However, the presence of one or more comorbidities did not seem to increase the risk of severe infections in ANK-treated patients. Notably, unusual or opportunistic infections (such as tuberculosis), which were reported in RA patients receiving anti-TNF-α therapies, were not observed in the progression of this study (10). The safety of treatment with ANK was also confirmed on 1346 patients with RA in a 6-month randomised double blind phase study comparing ANK (100 mg/day) with placebo, followed by an open label ANK treatment, extended for up to 3 years: throughout the study ANK was given concurrently with corticosteroids or methotrexate, and after 19 months of treatment only 1 patient receiving ANK in combination with prednisone and methotrexate experienced an atypical mycobacterial infection (11).

In addition, no case of active tuberculosis was recorded in over 4,000 patients with RA enrolled in several other studies (12-16), even when ANK was used in combination with supplementary biological agents (17). Furthermore, data from a Canadian registry have disclosed that the use of biological and traditional disease-modifying antirheumatic drugs is associated with increased risk of developing tuberculosis in patients with RA, mainly among those who did not use corticosteroids (18). In a cohort of 150 patients, including 71 with at least 18 months of follow-up, only 1 infectious adverse event was observed, but no confirmed case of tuberculosis (19). Finally, two anecdotal reports of Mtb reactivation under anakinra treatment were also observed: the first referred to the reactivation of a previous pulmonary Mtb infection in a patient with RA after 23 months of ANK monotherapy (100 mg daily), albeit there was no information regarding the correct adherence to antitubercular therapy (20), whilst the other one was based on a case of tuberculous pyomyositis in an elderly RA patient treated with ANK, who was not tested for tuberculosis prior to drug initiation, highlighting that screening for latent Mtb infection, including chest x-ray and tuberculin skin test or interferon-gamma release assay, is of utmost importance before starting any treatment with biological agents (21).

Systemic autoinflammatory disorders

Systemic autoinflammatory disorders (SAIDs) are a growing cluster of heterogeneous diseases characterised by apparently inexplicable recurrence of multi-organ inflammation in the absence of autoreactive T-lymphocytes and autoantibodies: they are caused by a lack of regulation in the inflammasome, a large intracellular multi-protein platform that plays a crucial role in innate immunity, leading to overproduction of proinflammatory cytokines, such as IL-1β, and to a pathological delay in the suspension of inflammatory responses (22, 23). Most SAIDs share a common clinical background, characterised by recurrent febrile attacks and inflammation involving different sites, such as skin, serosal membranes, joints, gastrointestinal or central nervous system: they include familial Mediterranean fever (FMF), mevalonate kinase deficiency syndrome (MKD), also known as hyperimmunoglobulinemia-D syndrome, TNF receptor-associated periodic syndrome (TRAPS), and the family of cryopyrin-associated periodic syndrome (CAPS), which in turn includes familial cold urticaria syndrome, Muckle-Wells syndrome (MWS), and neonatal onset multisystem inflammatory disease (NOMID).

The successful and safety profile of ANK has been clearly demonstrated in a wide range of SAIDs and also in several immune dysregulatory conditions not well defined at a genetic level (23). All CAPS are basically caused by gain-of-function mutations in the *NLRP3* gene and aberrant function of the NLRP3 protein, which are responsible for the inflammasome overactivation and abundant IL-1 release, requiring IL-1 inhibition as a first line treatment strategy (24). The first reported severe case of a child with NOMID treated with ANK dates back to almost 10 years ago (25), and data referred to the first observational study in 18 patients with NOMID who received ANK (1–2

mg/kg/day) were published in 2006, describing only upper respiratory infections (in 15 patients) as adverse events during 6 months of treatment. None of them developed tuberculosis (26). Neven *et al*. retrospectively analysed ANK efficacy and safety in 10 patients with NOMID for a period ranging from 26 to 42 months at a dosage of 1 mg/kg/day: no severe infections ensued, although it was speculated that IL-1 blockade might entail a possible risk of serious infections, even tuberculosis, especially in young children (27). A cohort of 26 patients with NOMID were treated with ANK (1–5 mg/kg/day) for 36–60 months: the main adverse events were upper respiratory infections, and the infection rate did not show a dose-dependent difference in patients treated with anakinra at a dose ≤2.5 mg/kg/day compared to patients treated with a dose >2.5 mg/kg/day. Despite infections ANK was continued, without reporting any case of tuberculosis (28). A single-centre observational study was performed on 12 patients with severe MWS (5 children and 7 adults), who received ANK for a median of 11 months, and no serious adverse event during the study period was observed: only mild infections in 5 patients occurred, and no case of tuberculosis (29).

FMF is considered the prototype of SAIDs and colchicine prophylaxis is the cornerstone of its treatment; however, approximately 5–10% of FMF patients do not respond to colchicine, and another 5% are intolerant because of side effects (30). Few data regarding the safety of ANK in FMF patients are currently available: a published FMF case series (4 adults and 2 children, all treated with ANK) has shown a potential risk of serious infections, especially in patients with comorbidities and in very young children with a poorly effective immune system against polysaccharide encapsulated bacteria (31). Similarly, several case reports have discussed about ANK safety in patients with colchicine-resistant FMF, even when ANK was used in combination with standard immunosuppression protocols (tacrolimus, mycophenolate, or prednisolone) in subjects who underwent kidney transplantation (32-37). The safety of ANK was also assessed in 5 TRAPS patients with severe disease course: neither major adverse reactions, nor severe infections were observed during treatment with ANK (38). In a small case series, 2 out of 7 patients with TRAPS receiving ANK up to 23 months experienced pharyngitis and bronchopneumonia, but no one developed Mtb infections (39).

Deficiency of IL-1 receptor antagonist (DIRA) syndrome is an exceptionally rare monogenic autoinflammatory syndrome, caused by mutations in the *IL-1RN* gene encoding an endogenous antagonist of IL-1 receptor, in which the inhibition of the IL-1 pathway has been proven effective and safe. In a case series of 6 patients with DIRA, ANK was administered empirically at a daily dosage of 1 mg/kg of body weight: the length of therapy varied between 2 weeks and 4.5 years, and patients did not experience infections of any kind (40). Furthermore, in accordance with data described in the medical literature (41, 42), the safety of ANK has been also demonstrated in a prospective observational study on 11 patients with MKD (2 with mevalonic aciduria and 9 with hyperimmunoglobulinaemia-D syndrome), albeit an increased frequency of mild upper respiratory tract infections was reported (43).

Schnitzler's syndrome

Schnitzler's syndrome (SchS) is a rare acquired autoinflammatory disease of adulthood, clinically characterised by urticarial skin rash, monoclonal gammopathy (mostly deriving from IgM kappa), and a variable combination of recurrent fevers, osteoarticular pain, sclerotic bone lesions, lymphadenopathy, and hepatosplenomegaly (44). Patients with SchS may develop haematological malignancies, such as Waldestrom's macroglobulinemia, and systemic reactive amyloidosis is an uncommon occurrence (45). Since IL-1β would seem to play a pivotal role in this disorder, anti-IL-1 agents such as ANK might represent the treatment of choice (46, 47). In this regard, several case reports have revealed the remarkable usefulness of ANK to reverse the clinical features of this disease, but long-term data concerning its efficacy, tolerance and safety are still insufficient. The largest series focusing on the management of these patients is a retrospective analysis from a multicentre cohort on 42 patients, of whom 29 were treated with ANK. The median follow-up under ANK treatment was 3 years, and 11 patients received ANK for more than 4 years: 6 patients experienced infections, including 1 case of sore throat and 5 cases of pneumonia; furthermore, 4 out of these 6 patients were also steroid-dependent before ANK treatment and had previously received high corticosteroid doses (>7,5 mg/d of prednisone), but no cases of tuberculosis were observed (48).

Behçet's disease

Behçet's disease (BD) is unanimously recognised as a chronic multisystem inflammatory disorder at the crossroad between autoimmune and SAIDs (49). The central role of innate immunity in its pathogenesis has been suggested by the increased levels of IL-1 in both serum and synovial fluid of BD patients, but also by the beneficial effects obtained with IL-1 inhibition. Although anti-TNF-α agents have been largely demonstrated to be effective in BD, this positive response might drop off over time (50, 51). In addition, the use of anti-IL-1 agents has proven to be safer than anti-TNF-α drugs, particularly in those geographical areas where tuberculosis is still a worrying global health issue (6). In this regard, recently we reported a case series dealing with 9 BD patients refractory to standardised therapies, who started daily ANK administration: this survey described the longest follow-up period ranging from 29 up to 114 weeks for BD patients treated with ANK, confirming both its prompt efficacy and safety. Indeed, no serious adverse events occurred in all 9 patients while on treatment with ANK, and tuberculosis cases were not observed (52). Interestingly, Bilginer *et al*. described a case of a teenage suffering from FMF and BD, who received ANK at the dose of 1 mg/kg/day subcutaneously along with colchicine treatment: the markedly positive tuberculin test in this patient was a concern for us-

ing anti-TNF treatment, and ANK was considered to be a safer option (53). Several BD cases have been reported showing the safe ANK administration also in relationship with different organ involvement (54-56). More recently we carried out the first and largest observational multicentre study aimed at evaluating for 24 months both efficacy and safety of anti-IL-1 agents ANK and canakinumab in 30 BD patients; among them 27 (90%) were treated with ANK and 3 (10%) with canakinumab: a very low number of side effects occurred during treatment with ANK, in all cases due to local cutaneous reactions, and no serious adverse events during the follow-up period. Our data have confirmed that the use of ANK is effective and safe showing a favourable profile in terms of risk of infection, and a low risk of tuberculosis reactivation, differently from TNF-α inhibitors (57). Of note, a pilot study – for which unfortunately there are not yet preliminary results – is now ongoing to assess the safety of ANK given at a daily dose of 100 mg with a dose escalation up to 200 mg daily (ClinicalTrials.gov NCT01441076). Further controlled trials on a larger number of BD patients are necessary to confirm the long-term safety profile of ANK regarding the risk of tuberculosis.

Adult-onset Still disease and systemic juvenile idiopathic arthritis

Adult-onset Still disease (AOSD) is a multisystem autoinflammatory disorder characterised by heterogeneous clinical features, including high-spiking fevers, evanescent skin rash, hepatosplenomegaly, lymphadenopathy, and polyarthritis (58, 59). The pathogenesis of AOSD is currently unclear, but the blockade of the IL-1 pathway has emerged as an effective therapeutic strategy since convincing evidences have shown that IL-1 could play a crucial role in its driving process (60). Notably, ANK as monotherapy has proven to be highly safe and effective in patients refractory to conventional treatments, such as corticosteroids or methotrexate. These findings rely not only on single case reports and small case series (61-75), but also on large numbers of subjects: a meta-analysis regarding the efficacy and safety of ANK was carried out analysing 8 studies, including a randomised controlled trial (76) and 7 observational studies (77-82) on 134 subjects suffering from AOSD. In all of the studies the dose of ANK was 100 mg/day. The sample size of each study ranged from 6 up to 28 patients. In all of the included studies ANK was well tolerated and not associated with increased risk of tuberculosis in any treated patients (83). Also systemic juvenile idiopathic arthritis (sJIA), which is the paediatric counterpart of AOSD, characterised by unremitting fevers associated with arthritis, evanescent rash, lymphadenopathy, hepatosplenomegaly, and polyserositis, underwent many changes in terms of treatment choices over the past decade with the improved understanding of the pathogenic role of specific proinflammatory cytokines, such as IL-1 (84). A major cause of morbidity and mortality of children with sJIA is the development of macrophage activation syndrome, which may be heralded by pancytopenia, coagulopathy, and hepatic dysfunction (85): for patients developing a life-threatening macrophage activation syndrome ANK could represent a promising therapeutic approach (86), but safety issues related to the risk of tuberculosis are actually unavailable.

Gout

Gouty inflammation is due to monosodium urate crystals which stimulate monocytes and macrophages to release IL-1β through the NLRP3 component of the inflammasome. The effectiveness of IL-1 inhibition in CAPS, caused by *NLRP3* mutations, suggested that IL-1 inhibition might also be useful in relieving the inflammatory features of acute gout (87). Over the last few years these observations contributed to the development of the first human trial with IL-1 antagonists among patients with gout: a pilot study tested the efficacy and safety of ANK among 10 patients who did not tolerate or had failed conventional treatments, such as nonsteroidal anti-inflammatory drugs, colchicine or corticosteroids; ANK was administered subcutaneously for 3 days, resulting in rapid and complete pain relief in 9 out of 10 patients within 48 hours, and this was in contrast to the incomplete response seen with the other currently available treatments. Notably, no ANK-related side effects were observed during the study, and there were no cases of tuberculosis or other infectious complications (88). Gouty occurs particularly in patients who frequently have associated comorbidities, that often limit the use of conventional therapy. In this regard Ottaviani et al. carried out a multicentre retrospective study examining data on 40 patients receiving ANK for gouty arthritis: 23 received ANK following the protocol used by So et al. (100 mg daily for three days subcutaneously) (88); 7 patients received ANK for <15 days (100 mg/day in 6 patients, and 100 mg every two days in 1 patient); the remaining 10 patients received ANK (100 mg/day) for the long term (>15 days). A total of 7 infectious complications, mainly staphylococcal infections, were reported in 6 patients, and 1 H1N1 viral infection occurred the day after ANK was started in another case; the other infectious complications occurred in patients with long-term use of ANK and were successfully treated with antibiotics. Of these 6 patients, 5 restarted ANK after the resolution of infection, and none of them presented any sign of tuberculosis (89). Ghosh *et al*. analysed a population of 26 hospitalised patients who were either resistant to standard therapy or had significant comorbidities that precluded the use of nonsteroidal anti-inflammatory drugs, colchicine and corticosteroids; ANK was given to 7 patients with perioperative gout flares and 4 patients receiving immunosuppressant drugs for organ transplantation or with underlying haematologic malignancy, but no adverse events occurred. Two patients under appropriate antibiotic treatment for infection (pneumonia and sepsis) underwent ANK courses without exacerbation of infection (90). Therefore, the use of ANK might be considered a valuable as well as safe therapeutic choice to treat acute gouty arthritis in such a medically complex population, with a relatively low risk of secondary infections.

Table I. Overview of data deriving from the medical literature dealing with anakinra safety in relationship with tuberculosis risk reactivation in various rheumatologic, metabolic and autoinflammatory disorders.

Disease	Study	Patients	Anakinra dose	Duration follow-up	Outcome of safety	References [Year]
RA	Randomised double-blind placebo-controlled	351	30, 75, or 150 mg/day	77 weeks	no relationship with severe infection risk	Nuki *et al*. [2002]
	Double-blind placebo-controlled	1116	100 mg/day	6 months	upper respiratory system infection and sinusitis	Fleischmann *et al*. [2003]
	Double-blind placebo-controlled	1116	100 mg/day	6 months	unusual or opportunistic infections such as tuberculosis were not observed	Schiff *et al*. [2004]
	Open label	1116	100 mg/day	3 years	1 atypical mycobacterial infection; 1 histoplasmosis; 1 *Candida* oesophagitis	Fleischmann *et al*. [2006]
	Double-blind	162	anakinra (100 mg/day) plus etanercept (25 mg twice weekly or 25 mg once weekly)	6 months	pneumonia and cellulitis (3 patients each), herpes zoster (1 patient), pneumonia (1 patient) and pyelonephritis (1patient)	Genovese *et al*. [2004]
	Observational	150	100 mg/day	24 months	1 Staphylococcus aureus sepsis	den Broeder *et al*. [2006]
	Case report	1	100 mg/day	23 months	reactivation of pulmonary tuberculosis	Settas*et al*. [2007]
	Case report	1	100 mg/day	11 years	tuberculous pyomyositis	Migkos *et al*. [2015]
NOMID	Observational	18	1-2 mg/kg/ day	16-17 weeks	15 upper respiratory infections, 2 urinary tract infections 1 nonbacterial diarrhea	Godbach-Mansky *et al*. [2006]
	Observational	10	1 to 10 mg/kg/day	26-42 months	no severe infections	Neven *et al*. [2010]
	Observational	26	1-5 mg/kg/day	36-60 months	2 wound infections, 1 macrophage activation syndrome, 1 post-traumatic hypopyon, 1 gastroenteritis	Sibley *et al*. [2012]
MWS	Observational	12	1-2 mg/kg/day	11 months	5 mild infections	Kuemmerle-Deschner *et al*. [2011]
FMF	Case series	6	100 mg/day 100 mg/48h 1 mg/kg/day	2-18 months	no severe adverse events	Meinzer *et al*. [2011]
TRAPS	Prospective	5	1.5 mg/kg/day	4–20 months	no major severe infections	Gattorno *et al*. [2008]
	Observational	7	100 mg/day	23 months	1 pharyngitis and 1 bronchopneumonia	Obici *et al*. [2011]
DIRA	Observational	6	1 mg/Kg/daily	2 weeks-4,5 years	no severe adverse events	Aksentijevich *et al*. [2009]
MKD	Prospective observational	11	1-2 mg/kg/day 100 mg/day	0.5–4 years	mild upper respiratory tract infections	Bodar *et al*. [2011]
SchS	Retrospective observational	29	100 mg/day	3-4 years	1 sorethroat and 5 cases of pneumonia	Néel *et al*. [2014]
BD	Case series	9	100-150 mg/day	13 months	no serious adverse events	Cantarini *et al*. [2013]
	Case report	1	1 mg/kg/day	12 months	no tuberculosis reactivation in a patient with reactive tuberculin test	Bilginer *et al*. [2010]
	Retrospective observational	27	100 mg/day	24 months	no serious adverse events observed	Emmi *et al*. [2015]
AOSD	Meta-analysis of 1 open label randomised and 7 observational	134	100 mg/day	24 weeks-7 years	no increased risk of tuberculosis in any treated patients	Hong *et al*. [2014]
Gout	Pilot	10	100 mg/day for 3 days	> 1 month	no infectious diseases	So *et al*. [2007]
	Multicentre retrospective observational	40	100 mg/day for 3 days; 100 mg/day < 15 days; 100 mg/day > 15 days	7 months	6 staphylococcal infections, 1 H1N1 viral infection	Ottaviani *et al*. [2013]
	Observational	26	100 mg/day for 1, 2, 3, 4 or 5 days; 200 mg/day for 5 days	–	a postoperative wound infection	Ghosh *et al*. [2013]
T1DM	Open-label pilot	15	50-100 mg/day	6 months	1 patient developed inguinal lymphadenopathy	Sumpter *et al*. [2011]
	Randomised double-blind placebo-controlled	35	100 mg/day	9 months	no development of tuberculosis	Moran *et al*. [2013]
T2DM	Double-blind parallel-group	34	100 mg/day	13 weeks	1 urinary tract infection and 1 upper respiratory tract infection	Larsen *et al*. [2007]

AOSD: Adult-onset Still's disease; BD: Behçet's disease; DIRA: Deficiency of the interleukin-1 receptor antagonist; FMF: familial Mediterranean fever; MKD: Mevalonate kinase deficiency syndrome; MWS: Muckle-Wells syndrome; NOMID: Neonatal-onset multisystem inflammatory disease; RA: Rheumatoid arthritis; SchS: Schnitzler's syndrome; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; TRAPS: Tumour necrosis factor receptor-associated periodic syndrome.

Type 1 and type 2 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder characterised by progressive destruction of pancreatic β cells, resulting in lifelong dependence from exogenous insulin administration, and risk of acute and late-term complications. Recent research has focused on the role of the innate immune system in T1DM: particular attention has focused on the role of the proinflammatory cytokine IL-1β, which is secreted by several cell types in response to tissue damage. There is a strong preclinical rationale to implicate IL-1 as an immune mediator of pancreatic β cell destruction leading to T1DM (91). An open-label pilot trial has shown how ANK given for 28 days in 15 children with new onset T1DM was well tolerated and even lowered insulin needs and glycated haemoglobin concentrations, if compared with historical controls: only a 14-year-old girl developed, as an adverse event, a bilateral tender inguinal lymphadenopathy on day 19 of therapy, without having fever or other signs of infection (then ANK was stopped, and her lymphadenopathy resolved spontaneously within 1 week) (92). Moran *et al*. tested the efficacy and safety of the anti-IL-1 agents ANK and canakinumab in two randomised placebo-controlled trials in two groups of patients with recent-onset T1DM. The ANK group reported significantly higher grades of dermatological and skin adverse events than the placebo group, however no cases of Mtb infection were observed (93).

Type 2 diabetes mellitus (T2DM) occurs when β cell function fails to compensate insulin resistance. Beta cells producing IL-1β have been observed in pancreatic sections obtained from patients with T2DM, and high glucose levels increase β cell production and release of IL-1β, followed by functional impairment and apoptosis (94). Indeed, under the influence of higher glycemic levels, pancreatic macrophages start to produce larger amounts of IL-1β which therefore might represent a therapeutic target for preserving β cell mass and function in patients with this condition (95). IL-1 receptor antagonist, a naturally occurring competitive inhibitor of IL-1 binding to the type I receptor, protects human β cells from glucose-induced dysfunction, and its expression is decreased in β cells obtained from patients with T2DM. Given these observations, Larsen *et al*. hypothesised that intervening in the islet balance between IL-1 receptor antagonist and IL-1β could improve β cell function and glycemic control in patients with T2DM. They designed a placebo-controlled double-blind parallel group study involving 70 patients with T2DM: patients received either once-daily 100 mg of ANK or placebo by subcutaneous self-administration for 13 weeks. Upper respiratory tract infection occurred in 1 patient, while tuberculosis was not found (96, 97). Despite these encouraging results, further studies on a broader number of patients with a longer observational follow-up periods are needed to consider ANK as a safe therapeutic choice in the treatment of T2DM.

Conclusions

The magnitude of the risk of opportunistic infections, particularly of Mtb infection, associated with the large use of ANK in many human diseases is actually unknown; in addition, it is unclear whether this effect is modified by the concomitant use of other antirheumatic drugs or corticosteroids. Conversely, it is well-known that TNF-α inhibition has been associated with risk of reactivation of tuberculosis and also with the development of different opportunistic infections. Table I lists the most recent data from the medical literature regarding safety issues for ANK in relationship with risk of tuberculosis in various rheumatologic, metabolic and autoinflammatory disorders. In particular, the rates of Mtb disease in patients with RA, SAIDs, SchS, BD, AOSD, sJIA, gout and DM treated with ANK have been low, and it is unestablished whether the concomitant use of disease-modifying antirheumatic drugs increases the risk of developing Mtb infection. Clinicians must carefully weigh the benefits of biologics against their risks, particularly in patients prone to infections. Additional data are needed to understand whether this risk of Mtb infection and reactivation are representative of a class effect related to biologics or whether ANK bears specifically an intrinsic lower risk in comparison with other biologic drugs.

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