Tuberculosis 118 (2019) 101863

Contents lists available at ScienceDirect

Tuberculosis

journal homepage: www.elsevier.com/locate/tube

Review

TB-IRIS pathogenesis and new strategies for intervention: Insights from related inflammatory disorders

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ARTICLE INFO

Keywords:
Tuberculosis
Human immunodeficiency virus (HIV)
Immune reconstitution inflammatory syndrome (IRIS)
Immunopathogenesis
Experimental therapeutics

ABSTRACT

In almost one in five HIV/tuberculosis (TB) co-infected patients, initiation of antiretroviral therapy (ART) is complicated by TB immune reconstitution inflammatory syndrome (TB-IRIS). Corticosteroids have been suggested for treatment of severe cases, however no therapy is currently licensed for TB-IRIS. Hence, there is a strong need for more specific therapeutics, and therefore, a better understanding of TB-IRIS pathogenesis. Immune reconstitution following ART is a precariously balanced functional restoration of adaptive immunity. In those patients predisposed to disease, an incomplete activation of the innate immune system leads to a hyper-inflammatory response that comprises partially overlapping innate, adaptive and effector arms, eventually leading to clinical symptoms. Interestingly, many of these pathological mechanisms are shared by related inflammatory disorders. We here describe therapeutic strategies that originate from these other disciplines and discuss their potential application in TB-IRIS. These new avenues of interventions range from final-phase treatment of symptoms to early-phase prevention of disease onset. In conclusion, we propose a novel approach for the discovery and development of therapeutics, based on an updated model of TB-IRIS pathogenesis. Further experimental studies validating the causal relationships in the proposed model could greatly contribute to providing a solid immunological basis for future clinical trials on TB-IRIS therapeutics.

1. Introduction

Despite being a preventable and curable disease, tuberculosis (TB) remains one of most common opportunistic infections in people living with HIV (PLHIV) as well as the most common cause of death [1–3]. Although antiretroviral therapy (ART) and subsequent immune reconstitution in PLHIV reduces the incidence of opportunistic infections such as TB, ART initiation can also trigger a pathological hyper-inflammatory response to viable or dead *Mycobacterium tuberculosis* (Mtb), known as TB immune reconstitution inflammatory syndrome (TB-IRIS). There is considerable clinical and pathophysiological heterogeneity in TB-IRIS, but cases are commonly divided into two main categories. Paradoxical TB-IRIS occurs when a previously diagnosed TB infection initially responds to TB therapy, but deteriorates upon ART-induced immune reconstitution. On the other hand, unmasking TB-IRIS is defined as the scenario in which a subclinical infection remains undiagnosed until ART-induced immune reconstitution triggers an excessively inflammatory presentation of the disease [4–6]. The pooled incidence of paradoxical TB-IRIS among co-infected patients initiating ART is estimated at 18%, but potentially higher in high-risk cohorts [7], with 25% of those patients requiring hospitalization [8].

Risk factors to developing TB-IRIS include (i) a low baseline CD4 T cell count before ART initiation; (ii) a short interval between TB treatment and ART initiation; and (iii) a high mycobacterial burden, also caused by disseminated TB [6,9–11]. Notwithstanding the global effort to increase early initiation of ART [3,12,13], PLHIV still often present with low CD4 counts, putting them at risk of TB-IRIS [14–17]. While in most cases the standard of care is to start ART later than 6–8 weeks after TB treatment initiation to avoid risk of TB-IRIS, several clinical trials showed that in those patients with a CD4 count < 50 cells/mm^3 overall mortality decreases when initiating ART within 2 weeks after initiation of TB treatment [10,18–21]. Despite the increased risk of developing TB-IRIS, this is now the recommended standard of care for those with very low CD4 counts [3]. TB-IRIS will therefore

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https://doi.org/10.1016/j.tube.2019.101863
Received 9 March 2019; Received in revised form 10 September 2019; Accepted 12 September 2019
Available online 13 September 2019

remain an issue in countries where both pathogens are endemic [9,10,14], indicating the need for greater understanding of its pathogenesis.

Prednisone treatment is currently the only therapeutic option for paradoxical TB-IRIS patients that is supported by clinical trial data [22]. Meintjes et al. showed a reduced median duration of required hospitalization as well as accelerated improvement of symptoms following a 4-week course of prednisone compared to placebo [23]. However, prednisone is not licensed for treatment of TB-IRIS and can be potentially harmful if used during insufficiently efficacious TB treatment [24]. Thus, while prednisone can be prescribed with caution, therapies that more specifically target the IRIS immune pathology are required.

Over the last few years, studies have revealed new information on the pathogenesis of TB-IRIS, and suggest an underlying mechanism of immunopathology that is shared with other syndromes. This opens up the road to a broader exploration of novel strategies for treatment and prevention. In the current review, we will discuss earlier models of TB-IRIS pathogenesis and summarize them into an overarching new model. Next, we will draw comparisons with related, non-infectious inflammatory diseases and review several recently postulated intervention strategies for potential future TB-IRIS management.

2. Pathogenesis of paradoxical TB-IRIS

2.1. TB-IRIS as a result of unbalanced functional restoration of adaptive immunity

The immunopathology of TB-IRIS was originally characterized as an overproduction of pro-inflammatory cytokines, in particular IFNγ, TNFα and IL-6 (hypercytokinaemia) [25–28]. As IRIS was first described in a cohort of PLHIV starting ART, the first model of TB-IRIS pathogenesis mentioned the repopulation of CD4 T cells during ART as the direct and central cause of the hypercytokinaemia [14,26,28–31]. While this cytokine storm (or hypercytokinaemia) is still considered to be the central part of TB-IRIS immunopathology, more recent studies showed that quantitative restoration of pathogen-specific CD4 T cell levels is not a pre-requisite for TB-IRIS development [29,32,33].

Interestingly, IRIS is increasingly being described also in non-HIV infected patients upon immune reconstitution following a period of iatrogenic immunosuppression. The most frequently described cases of non-ART IRIS occur following withdrawal of biological therapy such as anti-TNFα treatment or natalizumab, interruption of corticosteroid immunosuppression after solid-organ or hematopoietic stem cell transplantation [34–37] (Table 1). Other examples of IRIS have been reviewed and described elsewhere [38–41]. Although these occurrences of IRIS may seem highly diverse at first, the important common denominator is a situation of immune suppression that is independent of CD4 T cell count, combined with the presence of antigen. Thus, IRIS should be seen as a result of functional restoration of the adaptive immune system.

Considering the important role the adaptive immune system serves in the defence against pathogens, a functional reconstitution of adaptive immunity in TB/HIV co-infected people would in principle be beneficial. Other, underlying mechanisms must therefore exist that tip the balance of the otherwise beneficial immune reconstitution into IRIS immune pathology.

2.2. Predisposition to TB-IRIS due to uncoupling of innate and adaptive immunity

Barber et al. were one of the first to propose a model for the underlying mechanism of this unbalanced immune reconstitution [42]. Their model links the traditional risk factors for TB-IRIS (see section 1. Introduction, [9–11]) to the process of incomplete activation of innate immunity and explains how this leads to a state of predisposition to TB-

Table 1
Examples of the variety of IRIS manifestations and possible etiologies. The common denominator in all forms of IRIS is a state of immunosuppression that is reverted, combined with the presence of antigen.

Form of IRIS	Source of antigen	Immunosuppression	Underlying disease	Cause of immune reconstitution	Ref.
TB	Bacterial – *Mycobacterium tuberculosis*	Low CD4 T cell count	HIV-infection	ART initiation	[30]
TB Meningitis	Bacterial – *Mycobacterium tuberculosis*	Low CD4 T cell count	HIV-infection	ART initiation	[103]
TB	Bacterial – *Mycobacterium tuberculosis*	TNFα-blockade (infliximab, adalimumab, etanercept)	RA, sarcoidosis, psoriasis (among others)	Withdrawal of anti-TNFα	[37]
PML	Viral - JC virus	Low CD4 T cell count	HIV-infection	ART initiation	[64,104]
PML	Viral - JC virus	α4-integrin-blockade (natalizumab)	MS	Withdrawal of natalizumab	[64,105]
KS	Viral – HHV-8	Low CD4 T cell count	HIV-infection	ART initiation	[106]
Cryptococcal	Fungal – *Cryptococcus neoformans*	Prednisone	Solid-organ transplant	Withdrawal of prednisone	[107]
Cryptococcal Meningitis	Fungal – *Cryptococcus neoformans*	Low CD4 T cell count	HIV-infection	ART initiation	[61]
Candidiasis	Fungal – *Candida spp*	Chemotherapy	Haematological tumour	HSCT	[107]

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; HHV-8, human herpes virus 8; HSCT, hematopoietic stem cell transplantation; IRIS, immune reconstitution inflammatory syndrome; KS, Kaposi's sarcoma; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; RA, rheumatoid arthritis; Ref, reference number; TB, tuberculosis.

IRIS. As mentioned previously, a low baseline CD4 count before ART initiation and the resulting dysfunctional adaptive immune system form a strong risk factor for TB-IRIS [9–11]. Due to lower IFNγ levels pre-ART in these individuals [33], activation of infected monocytes and macrophages in these patients remains incomplete [42]. This process, the so-called uncoupling of the innate and adaptive immune system, would lead to accumulation of antigen in these innate cells and builds up a state of hyper-responsiveness to future immune activation [42]. Meanwhile, short intervals between TB treatment and ART initiation, as well as the presence of disseminated disease contribute to a high antigen burden [9]. Furthermore, a recent study suggested a role herein for CD8 and NK cells, by showing increased immune exhaustion in these cell subsets before ART initiation in individuals that developed TB-IRIS as compared to $HIV^{+}TB^{+}$ controls [43]. As both CD8 T cells and NK cells are involved in the clearance of intracellular pathogens, immune exhaustion in these cell subsets could contribute to accumulation of antigen prior to ART initiation [43]. Upon functional restoration of the adaptive arm, as will occur with ART initiation, the sudden activation of the infected monocytes would lead to an explosion of inflammatory cytokines and subsequent onset of TB-IRIS [42]. While this theory was originally based on a murine model of *Mycobacterium avium*-IRIS, the authors later provided supportive evidence by reporting similar results on the role of myeloid cells pre-ART in TB-IRIS patients [44]. These results are in agreement with Goovaerts et al., who reported lower levels of CD8 T cell activation pre-ART due to the inability of the innate immune system to initiate an effective response to Mtb antigen [45]. Altogether, predisposition to TB-IRIS occurs through an interplay of the traditional risk factors for TB-IRIS and is suggested to involve the uncoupling of the innate and adaptive immune system (Fig. 1).

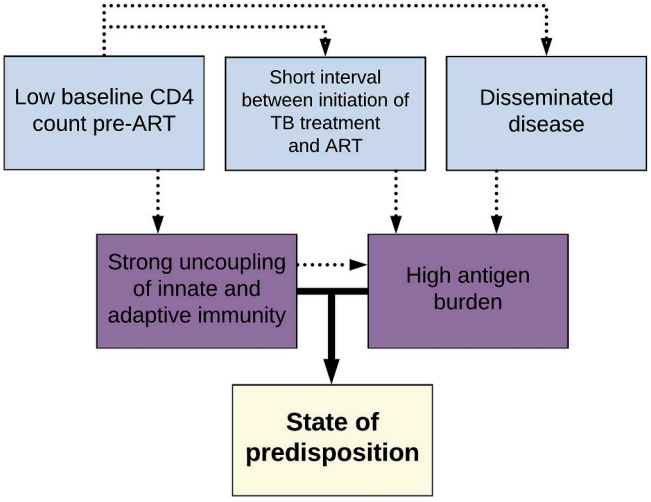

Fig. 1. Predisposition to TB-IRIS is caused by uncoupling of innate and adaptive immunity The various known risk factors for TB-IRIS (top, blue) give rise to a state of predisposition that unbalances the immune reconstitution through the process of uncoupling of innate and adaptive immunity [42]. Low baseline CD4 count pre-ART is one of the main factors associated with increased risk of TB-IRIS (blue). A low CD4 count pre-ART is a reason for faster ART initiation, leading to a shorter interval between TB treatment and ART initiation, the second commonly accepted risk factor. In addition, disseminated disease is more likely to occur in those with low CD4 count. Following the model proposed by Barber et al. low baseline CD4 counts (and thus strong immunosuppression) lead to strong uncoupling of the innate and adaptive arms of the immune system. Meanwhile, a short interval between initiation of TB treatment and ART leads to a higher antigen burden at time of ART initiation, further aggravated in patients with disseminated disease. Together, the uncoupling of innate and adaptive immunity and the high antigen burden (purple) cause a state of hyperresponsiveness to immune activation (state of predisposition, yellow) that will unbalance an otherwise beneficial immune reconstitution to a pathological one, leading to TB-IRIS. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.3. Innate immune activation as the first arm of TB-IRIS pathogenesis

Several studies have suggested that the initial phase of TB-IRIS pathogenesis is mediated by myeloid cells of the innate immune system [46,47]. In a whole-blood transcriptomic profiling study, Lai et al. found three innate signalling pathways (TLR, TREM-1 and IL-1) to be most enriched in TB-IRIS [48]. These transcripts were already overabundant as early as 0.5 weeks after ART initiation, i.e. before the onset of any clinical symptoms, suggesting these pathways represent the earliest mechanisms underlying the development of TB-IRIS.

The involvement of the inflammasome is proposed as a common downstream effect of the enriched TREM-1 signalling [48]. Inflammasomes are important mediators of immune activation by cleaving and thereby activating innate cytokines such as IL-18, a member of the pro-inflammatory IL-1 family of cytokines [49,50]. The role of inflammasomes, in particular NLRP3 and AIM2, in TB-IRIS was confirmed by studies that identified IL-18 as a biomarker and predictor of TB-IRIS [33,49,51]. Activation of NLRP3 and potentially other inflammasomes is negatively regulated by NO and IFNγ, which are both decreased in TB-IRIS patients pre-ART, potentially resulting in a lack of inflammasome control [49]. Given the role of inflammasomes in membrane rupture and release of antigenic content [49], they are believed to act synergistically with TLR and IL-1 receptor signalling to amplify the innate immune response.

In addition to the myeloid compartment, several studies have suggested the involvement of other innate immune cell types in TB-IRIS onset, including those that bridge the gap between innate and adaptive immunity [52–55]. In those individuals that went on to develop TB-IRIS, NK cell degranulation levels were shown to be significantly higher at baseline (pre-ART initiation) and potentially also at TB-IRIS onset [52,53]. Increased levels of killer immunoglobulin receptor $(KIR)^{-}$ $V\delta2^{+}TCR\gamma\delta^{+}$ T cells at baseline were reported by one study, implying a role in amplifying the dysregulated immune response [55]. However, others found reduced proportions of these cells in TB-IRIS, and instead attributed the increased cytotoxicity and perforin release in TB-IRIS to increased proportions of invariant NKT cells [54]. Indeed, increased numbers of circulating invariant NKT cells have been associated with TB-IRIS, as well as increased invariant NKT cell degranulation at time of TB-IRIS onset [56]. However, the precise contribution of these cell types and how they interplay with the myeloid cells still needs to be elucidated.

Taken together, early TB-IRIS pathogenesis is mediated by innate immune activation characterized by inflammasome activation, IL-18 and TLR signalling (Fig. 2, top arrow) following ART initiation. Follow-up studies on the role of cell types cross-linking innate and adaptive immunity will be required to confirm how these can be integrated into the latest models of TB-IRIS pathogenesis (Fig. 2, small arrow). The mechanisms through which ART and subsequent viral suppression lead to activation of these particular innate inflammation pathways remain unclear and will need to be further investigated.

2.4. Adaptive immune activation leads to amplification of early pathogenesis

The increasing evidence for innate immune involvement should be seen as an addition to the original T cell centered model for TB-IRIS. TB-IRIS is characterized by the expansion of pathogen-specific T cells, resulting in increased detection of already present antigen, and a state of hypercytokinaemia as discussed above [25–28,31]. However, these events should be seen as the secondary step in TB-IRIS pathogenesis rather than being the central contributory factor (Fig. 2, middle arrow).

It has been hypothesized that a disturbance of regulatory T (Treg) cell compartments could explain the excessive inflammation and hypercytokinaemia, however conflicting results have been reported in this

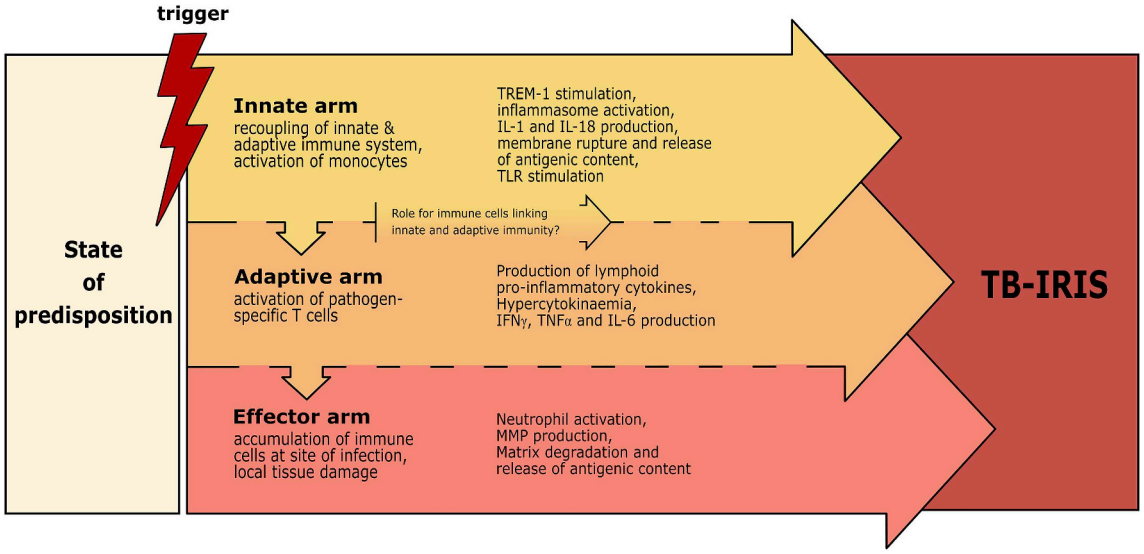

Fig. 2. Integrated model for TB-IRIS pathogenesis TB-IRIS can develop in those patients predisposed pre-ART. Immune reconstitution upon ART initiation serves as the trigger initiating a range of events, which can be divided into three main arms. Recoupling of the innate and adaptive immune system leads to full activation of infected monocytes and macrophages, which leads to inflammasome activation, IL-1 and IL-18 production and release of antigenic content that further stimulates the innate immune system via TLR. The pro-inflammatory cytokines IL-1 and IL-18 will activate the adaptive immune system, further stimulating expansion of pathogen-specific lymphocytes, and production of (myeloid and) lymphoid pro-inflammatory cytokines such as IFNγ, TNFα and IL-6 (hypercytokinaemia). The pro-inflammatory environment will contribute to expansion of pathogen-specific T cells and migration of lymphocytes to the site of inflammation, amplifying the effect of immune reconstitution. In addition, NKT and γδT cells have been suggested to contribute to TB-IRIS pathogenesis as cross-linkers of innate and adaptive immunity, but their exact role still needs to be elucidated. The accumulation of immune cells will activate local effector cells such as neutrophils, which contributes to tissue damage via MMP production. The subsequent release of antigenic content further activates innate signalling pathways, again amplifying the response. These three arms of pathogenesis act in synergy, eventually adding up to a pathological state defined as TB-IRIS.

regard (reviewed by Refs. [38,57,58]). Instead of an expected decrease in Treg cells, several studies have shown equal or even increased numbers, but decreased functionality, of Treg cells in IRIS patients at baseline compared to non-IRIS controls [28,29,59–63]. In addition, there is controversy as to the kinetics of Treg numbers upon immune reconstitution [28,60]. Further studies on the role of regulatory T cells are required to confidently incorporate their function into a model of TB-IRIS pathogenesis.

A role for leukocyte migration has been proposed following the description of progressive multifocal leukoencephalopathy (PML)-IRIS in MS patients upon withdrawal of natalizumab, a leukocyte trafficking inhibitor [64] (Table 1). High numbers of CCR5+ cells were found in these PML-lesions, indicating the role of this chemokine receptor in lymphocyte migration and subsequent immunopathology [65,66]. It could thus be hypothesized that the pro-inflammatory environment and T cell expansion is followed by migration of these lymphocytes to the site of infection, amplifying the innate immune activation.

2.5. Effector arm in TB-IRIS pathogenesis induces local tissue damage

The most recent advances in TB-IRIS pathogenesis have focused on the effectors of tissue damage that contribute to clinical symptomatology. Neutrophil dysfunction as well as matrix metalloproteinases (MMPs) have been recognized in pulmonary symptoms of non-HIV TB pathology, and both are increasingly studied for their role in TB-IRIS immunopathology [51,67–69]. MMP8 is pre-synthesized by neutrophils and stored in granules and causes tissue damage by releasing matrix degradation products upon secretion [70,71]. Neutrophils were found to accumulate in areas of cell death within the site of disease and showed a higher level of activation and subsequent toxic granule release than in non-IRIS controls [67]. These findings are confirmed by Walker et al. who propose a model in which Mtb induces MMP activity during TB-IRIS and subsequent enhanced MMP leads to matrix degradation and release of systemic antigen, further amplifying the inflammatory response [72] (Fig. 2, bottom arrow).

2.6. Reformulation of the old models of TB-IRIS pathogenesis

Upon initiation of ART in HIV/TB co-infected patients, immune reconstitution will be beneficial in the majority of cases, reverting immunosuppression and restoring the anti-TB immune response. However, in those patients predisposed to TB-IRIS, the balance will gradually shift from beneficial immune reconstitution to a pathological, excessively inflammatory immune response. Predisposition occurs when (i) there is a low nadir CD4 count, resulting in strong uncoupling of the innate and adaptive immune system; leading to (ii) a high antigenic burden due to a lack of full activation of infected monocytes and lack of inflammasome inhibition, a short interval between TB treatment and ART initiation and disseminated disease (Fig. 1). Based on the newly identified mechanisms described above, we propose the following model for TB-IRIS pathogenesis. Upon triggering by immune reconstitution, these combined events lead to inflammasome activation, membrane rupture and release of antigenic content, TLR stimulation and subsequent activation of the now recoupled adaptive immune system. This contributes to the expansion of pathogen-specific T cells, production of pro-inflammatory cytokines and chemokines, initiating a positive feedback loop of further activation, attraction of more immune cells to the site of inflammation, cell death and release of antigenic content. This state can eventually be characterized as one of hypercytokinaemia with the main upregulated cytokines being TNFα, IL-6 and IFNγ. The inflammation causes tissue damage specific to the site of infection, which is further amplified by neutrophil MMP release and matrix degradation (Fig. 2).

Although the processes in this model of TB-IRIS immunopathology are initiated by the presence of pathogenic antigen (Mtb), it is mainly the host immune response that causes the clinical symptomatology. These common host immune processes may also be related to other immunological disorders involving excessive inflammation; be it other forms of IRIS or types of auto-immunity. In the next section, we will explore these similarities and discuss what could be learned for novel TB-IRIS management strategies.

Table 2
Exploration of potential therapeutic interventions for TB-IRIS.

Name	Level of intervention	Mechanism of action	Related disease	Ref.
Tadekinig alpha	Innate arm	IL-18BP	RA, hypersensitivity, type 1 diabetes, MS	[33,50]
MCC950	Innate arm	inflammasome inhibition	MS	[75–77]
Biologic therapy	Adaptive arm	Inhibit TNFα or IL-6	RA	[14,27,58,79,80]
Doxycycline	Effector arm	Neutrophil and MMP inhibition	HIV- TB, periodontal disease	[32,81–83]
Maraviroc	Adaptive arm/migration	CCR5 inhibition	HIV, PML-IRIS in MS	[66,86,87]
Statins	All-arm	Broad mechanism of action	GVHD	[95]

Abbreviations: CCR5, C–C chemokine receptor 5; GVHD, graft-versus-host-disease; HIV- TB, non-HIV associated TB; IL-18BP, IL-18 binding protein; MMP, matrix metalloproteinase; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; RA, rheumatoid arthritis; Ref, reference number.

3. Management strategies for TB-IRIS

When designing new management strategies for TB-IRIS, interventions may be aimed at the various levels of pathogenesis (Fig. 2). The proposed therapeutic interventions discussed below are summarized in Table 2.

3.1. Attenuation of excessive innate immune activation

A first approach would be to prevent the onset of excessive inflammation by targeting the innate mediators of early pathogenesis, IL-18 and IL-1β being the strongest candidates [33,73].

Biological therapeutics targeting IL-1 are licensed for rheumatoid arthritis (anakinra) and auto-inflammatory syndromes (canakinumab, rilonacept). These biological agents are being studied for use in other IL-1-associated diseases [74], and hence a potential role for these drugs in TB-IRIS has been suggested [48]. A recent study by Nouhin et al. indeed reported elevated levels of IL-1 receptor antagonist at the time of TB-IRIS onset, but hypothesized that this increase was insufficient to regulate monocyte/macrophage activation. The recombinant IL-1 receptor antagonist anakinra, as well as the other biological agents targeting this pathway, could thus potentially be of use in TB-IRIS [73].

In vivo, IL-18 is directly regulated by IL-18BP, which prevents Th1-mediated inflammation by captivating free circulating IL-18. Inadequate regulation of IL-18 by IL-18BP is suggested to play a role in TB-IRIS, which is associated with higher levels of free IL-18 [33]. In line with these findings, IL-18BP treatment is implicated as beneficial in inflammatory or auto-immune diseases such as rheumatoid arthritis, contact hypersensitivity, type 1 diabetes and Multiple Sclerosis (MS) [50]. A Phase III clinical trial is ongoing to assess drug efficacy of an exogenous recombinant human IL-18BP in reducing flares in a cohort of monogenic, IL-18 driven auto-inflammation (ClinicalTrials.gov Identifier: NCT03113760). Considering IL-18 levels in TB-IRIS patients are elevated already before ART initiation [33], this treatment could be prescribed before disease onset to prevent severe IRIS requiring hospitalization. Measurements of free IL-18 would allow continuous monitoring of treatment efficacy.

An alternative strategy for targeting the IL-18/IL-1β signalling pathway would be to inhibit the production of active IL-18/IL-1β by preventing cleavage by the inflammasome [48–51]. By targeting this more upstream mediator of both IL-18 and IL-1β signalling, both of which are associated with TB-IRIS, the effect is likely to be more substantial than targeted blockade of IL-18 or IL-1β alone [50]. As reviewed by Fenini et al. several small molecule inhibitors targeting inflammasomes are being investigated, among which the most promising, MCC950 [75]. In vitro, MCC950 was able to inhibit activation of the NOD-like receptor (NLR) family pyrin domain–containing protein 3 (NLRP3) inflammasome in response to LPS stimuli [76]. While both NLRP3 and AIM2 are transcriptionally upregulated in TB-IRIS, inhibition of NLRP3 alone could potentially inhibit both inflammasomes: AIM2 responds to dsDNA stimuli and thus, AIM2 involvement is most likely downstream of NLRP3-induced pyroptosis and release of Mtb dsDNA [49]. In a mouse model for human MS, in which pathology is dependent on NLPR3 activation (similar to TB-IRIS), MCC950 delayed onset and severity of the autoimmune disease [77]. Importantly, MCC950 does not inhibit two main other inflammasome subtypes, NLRC4 and NLRP1, nor TLR signalling, which play an important role in antimicrobial defence [76]. This suggests that, while MCC950 does act in a very upstream part of the pathogenic cascade of TB-IRIS, it may have fewer general immunosuppressive effects than corticosteroids [78]. Furthermore, a small molecule inhibitor such as MCC950 may be more cost-effective than other drugs, such as the frequently suggested biologics (see below). Small molecules also have a shorter half-life, which would allow faster drug withdrawal upon establishment of potential adverse events [76]. Further research on the exact role of the different inflammasomes in TB-IRIS pathogenesis will be required to assess whether inhibition of NLRP3 alone would be sufficient to dampen IL-18/IL-1β signalling.

3.2. Targeting the adaptive and effector arms of TB-IRIS pathogenesis

An alternative approach would aim to more specifically treat the hypercytokinaemia and tissue damage that characterize TB-IRIS, thus treating symptomatology after the onset of disease. While we have seen that prednisone is effective at this stage, more targeted approaches are desirable [14,23].

These could include antibody targeting of TNFα and IL-6, the most consistently upregulated cytokines during TB-IRIS, a treatment strategy that has been suggested frequently [14,27,58,79,80]. TNFα and IL-6 inhibition are commonly used for the treatment of autoimmune diseases such as rheumatoid arthritis. Notwithstanding its theoretical benefits in TB-IRIS, such biological therapy is associated with high costs and potential side effects due to strong immunosuppression induced by these drugs. These considerations may limit the feasibility of these treatment strategies in TB-IRIS.

Host-directed therapies targeting tissue damage could focus on neutrophil activation and recruitment, or MMP production. As for the latter, doxycycline is licensed as an MMP inhibitor and extensively studied for the treatment of TB (with and without HIV co-infection) [81]. While doxycycline is a common antibiotic drug, of specific interest here is its use in treating periodontitis [82,83]. Periodontitis is an inflammatory disease extraordinarily similar to TB-IRIS, characterized by a dysbiotic biofilm of pathogens on the tooth surface followed by an inflammatory reaction [84], characterized by connective tissue degradation [82]. In addition to acting as a direct antimicrobial agent, doxycycline also suppresses TNFα secretion [81,82]. A 3D model of TB granuloma formation has shown inhibition of TB-induced matrix degradation by doxycycline [32], suggesting its potential use in the treatment of TB-IRIS. Doxycycline is widely available at low-cost and is relatively safe, which may increase the feasibility of clinical application in resource-limited settings. The strong benefit of an MMP-directed approach for TB-IRIS over systemic immunosuppression is that there is less risk of other opportunistic infections.

In addition to targeting specific cytokines or their upstream mediators, it has been suggested to target the CCR5-mediated chemo-attraction of immune cells to the site of inflammation, thereby preventing the amplification of the immune response and subsequent hypercytokinaemia. To this aim, the use of maraviroc, a CCR5 inhibitor and antiretroviral drug, has been suggested. Several case reports support this suggestion [85,86]. These were followed by the CADIRIS trial, a large

clinical trial studying the protective effects of an ART regimen with or without maraviroc on development of IRIS in general [87]. No difference was found in emergence, severity or timing of IRIS events between ART with maraviroc or ART alone. The study did not have sufficient power to discriminate between specific pathogen-related forms of IRIS, such as TB-IRIS, and thus a stronger role for CCR5 in specific forms of IRIS may have been missed [87]. Further research in the differential pathogenesis and CCR5 involvement in various forms of IRIS will be needed to support this hypothesis and support further studies on maraviroc as a potential therapeutic for TB-IRIS.

3.3. Non-specific immunosuppression to treat TB-IRIS

While the above-described treatment strategies target a specific mediator or pathway, the last therapeutic that has recently been suggested can be categorized as a broad immunosuppressant [88]. Statins are widely prescribed for their cholesterol-lowering properties in cardiovascular disease, but have increasingly been studied for their immunomodulatory effects [88,89]. Studies initially focused on atherosclerosis-associated inflammation, but were later expanded to autoimmune diseases and, interestingly, graft-versus-host-disease (GVHD) after allogeneic hematopoietic stem cell transplantation [90]. GVHD pathology shows similarities to IRIS in that it is characterized by an excessive immune response from the reconstituting donor immune system towards a high antigen burden. GVHD is not associated with any pathogen, but is triggered by ubiquitous host antigen that is recognized as foreign by the reconstituting donor immune system [90,91]. Analogous to TB-IRIS, pathology in GVHD is associated with inflammasome activation and a subsequent cytokine storm [91]. Statins increased survival in a mice model of GVHD [92] as well as reduced onset of GVHD in human allogeneic transplant patients [93]. The immunosuppressive mechanism of action for statins is very broad [88], but of primary interest for treatment of TB-IRIS is their inhibition of MHC-II antigen presentation and co-stimulatory molecule expression [88], induction of regulatory T cell development [90], reduction of MMP levels and induction of neutrophil apoptosis [94]. Through these mechanisms, statins could respectively target the recoupling of innate and adaptive immunity (innate arm, see Fig. 2), dampen hypercytokinaemia (adaptive arm) and reduce tissue damage (effector arm) in TB-IRIS. Furthermore, several studies have shown that, although acting as a broad immunosuppressant, statins do not interfere with the immune response to pathogens [90,95] and may even have a positive role in treatment of infection [96]. Altogether, statins may potentially be good candidates for TB-IRIS treatment [95].

3.4. Management of TB-IRIS by preventive treatment

An alternative approach would be to administer general prophylaxis to co-infected PLHIV starting ART to prevent pathogenesis. Following up on the highly promising results of the clinical trial on the use of prednisone for the treatment of TB-IRIS [23], the PredART trial studied the effects of a prophylactic course of low-dose prednisone for high-risk co-infected PLHIV upon ART initiation [97]. Their results show a decrease of TB-IRIS incidence from 46.7% in the placebo arm to 32.5% in the prednisone arm, corresponding to a relative risk of 0.70 (95% confidence interval: 0.51–0.96) [97]. No excess risk of opportunistic infection or malignancy was reported. Since the 30% lower incidence of TB-IRIS in the prednisone group was smaller than predicted, it is suggested further research could evaluate higher doses of prednisone or targeting preventive therapy to those patients at high risk of TB-IRIS [97].

Secondly, statins are also promising candidates for preventive treatment. Prophylaxis with statins in animal models of GVHD and MS reduced onset and severity of disease [92,98]. Prescription of statins for their cholesterol-lowering properties in PLHIV is very common and was not associated with adverse events [99,100], potentially allowing more rapid clinical testing to assess potential benefits in preventing TB-IRIS onset. However, statins were associated with blunting of CD4 T cell immune reconstitution upon ART initiation despite sustained virologic response to ART, which should be further evaluated in future studies [101].

4. Concluding remarks

ART-induced IRIS should be seen as a result of functional restoration of adaptive immunity that is also observed after non-HIV-related immunosuppression. In fact, many of the immunological processes involved in the pathogenesis of TB-IRIS are shared by other, non-infectious inflammatory disorders or auto-immune diseases. Such similarities allow us to adopt treatment strategies from these related fields as potential new therapeutic interventions for TB-IRIS. These findings once more indicate the importance of combining research activities in inflammatory disorders and infectious diseases to tackle global health issues.

We have proposed an integrated model of TB-IRIS pathogenesis. It should be noted that the causal relationships proposed in our model are speculative, as we base our model mainly on correlative rather than experimental data. Further experimental research is required to build a chronological model of pathogenesis including causal relationships. Secondly, while the innate and adaptive immune response are depicted as separate arrows, reports on the role of innate cells bridging innate and adaptive immunity indicate that significant overlap exists [52–55]. Further research in this area will allow for better incorporation of these innate cell subsets into the model of TB-IRIS pathogenesis.

When discussing TB-IRIS prophylaxis, it is important to remember that the immune reconstitution upon ART initiation is a precarious balance, as discussed above. TB-IRIS is a result of the unbalancing towards the hyper-inflammatory side of the spectrum, which could theoretically be prevented by immunosuppressive prophylaxis. An inherent aspect of prophylaxis is that its immunosuppressive effects will also apply to those patients that would otherwise have followed a non-inflammatory and well-balanced immune reconstitution. Imprudent use of prophylactic immune modulators in such patients may result in adverse outcomes [102]. Clinical trials assessing general immunosuppression and prophylaxis should monitor these.

Lastly, a validated diagnostic test for TB-IRIS is still lacking but would be extremely valuable. Concurrent with the above-described advances, significant efforts are being made to identify both prognostic and diagnostic biomarkers [22]. The identification of those at high risk of developing TB-IRIS or grading its likely severity would allow for targeting of (preventive) interventions and use of more expensive modalities. Successful earlier treatment of HIV in TB endemic areas where the likelihood of TB/HIV coinfection is high would be greatly enhanced by further research and innovation in TB-IRIS.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors have no competing interests to declare.

Acknowledgements

We would like to thank Graeme Meintjes for his critical review of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tube.2019.101863.

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