Tuberculosis IRIS

Subjects: Others

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Antiretroviral therapy (ART), while essential in combatting tuberculosis (TB) and HIV coinfection, is often complicated by TB-associated immune reconstitution inflammatory syndrome (TB-IRIS). Depending on the TB diagnosis and treatment status at ART initiation, this immune-mediated worsening of TB pathology can take the form of paradoxical TB-IRIS, unmasking TB-IRIS. Each form of TB-IRIS has unique implications for diagnosis and treatment. This entry is a discussion of TB-IRIS with an expanded focus on CNS TB-IRIS given its severe outcomes and anatomic and immunologic peculiarities.

Keywords: Tuberculosis ; Tuberculosis meningitis ; Immune reconstitution inflammatory syndrome ; TB IRIS ; Paradoxical IRIS ; unmasking IRIS ; TB meningitis IRIS

1. Introduction

Mycobacterium tuberculosis infection (TB) remains the world's most deadly infectious disease with 10 million cases and nearly 1.5 million deaths in 2018 alone [1]. TB burden remains highest in parts of the world with high HIV prevalence—notable, given that TB and HIV co-infection negatively affects patient outcomes. TB infection leads to increased HIV replication and HIV contributes to TB progression due to HIV mediated immune suppression [2]. People living with HIV have a 19 times increased risk of developing TB, and make up 17% of all TB deaths worldwide [1]. TB accounts for one in three AIDS-related deaths, making it the leading contributor to mortality in people living with HIV [1].

The roll-out of anti-retroviral therapy (ART) in settings with high TB and HIV prevalence has been instrumental in combatting these twin epidemics, with ART availability reducing TB risk by 58–80% [3]. Since 2000, TB mortality in HIV-positive individuals decreased by 60% compared to 27% among HIV-negative individuals—almost certainly in part due to wider ART availability [1]. However, an important complication of TB-HIV coinfection in the post-ART era is TB-associated immune reconstitution inflammatory syndrome (TB-IRIS). First recognized in the years after the roll-out of ART, this syndrome is characterized by severe inflammatory features of TB occurring after rapid reconstitution of the immune system once ART has been initiated. This should be distinguished from TB paradoxical reaction (also sometimes referred to as IRIS though these are not the same phenomena), a long-recognized feature of the course of TB treatment where there is a brief paradoxical worsening of symptoms after initiating TB treatment, that is independent of rapid immune recovery caused by ART [4][5]. In 2006, the need to standardize terminology used for TB-IRIS [6][7][8] motivated the International Network for the Study of HIV associated IRIS (INSHI) to establish the currently-used consensus case definitions for the two different forms of TB-IRIS—paradoxical and unmasking (Figure 1) [4].

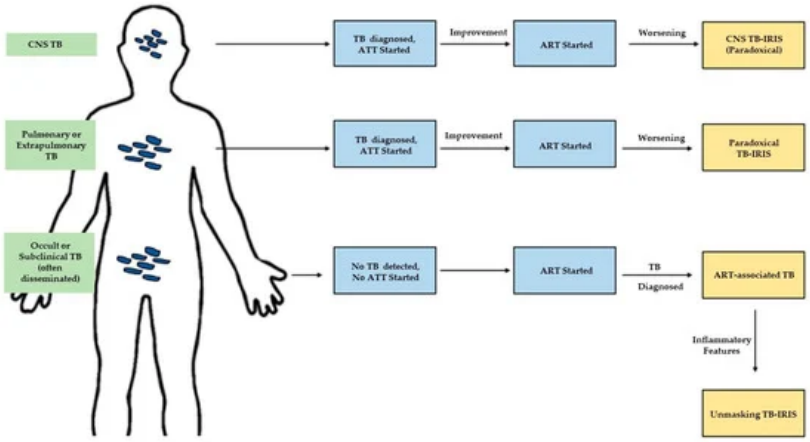

Figure 1. Diagnostic categories of TB-associated immune reconstitution inflammatory syndrome (TB-IRIS).

Diagnostic categories of TB-IRIS depend on the sequence of ATT (antitubercular therapy) and ART (antiretroviral therapy) initiation, as well as the site of TB at ART initiation. Paradoxical IRIS is diagnosed when pulmonary or extrapulmonary TB worsens after ART initiation in a patient who previously responded to ATT. ART-associated TB is any TB diagnosed after ART initiation, while unmasking TB-IRIS is a subcategory where the TB presentation is markedly inflammatory. We add a final major category of CNS-TB-IRIS based on its unique pathologic and therapeutic considerations.

Paradoxical IRIS is the onset of IRIS manifestations within three months of ART initiation in a patient previously diagnosed with TB and with an initial response to treatment. Manifestations include enlarging lymph nodes, cold abscesses, worsening radiological features, worsening serositis, or worsening of symptoms of at least two diseases locations (i.e., constitutional symptoms, respiratory symptoms, abdominal symptoms) [4].

ART-associated TB is active TB diagnosed after ART initiation in a patient not receiving TB treatment.

Unmasking TB-IRIS is ART-associated TB that occurs within three months of ART initiation and has a “heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component”. Examples include, but are not limited to, lymphadenitis, abscesses, respiratory failure, or a systemic inflammatory syndrome. Importantly, in this case TB was not diagnosed or treated prior to initiation of ART [4].

The definition for paradoxical IRIS is well characterized and has been widely used, but the definition for unmasking IRIS remains provisional due to an unclear delineation of the inflammatory characteristics required, and therefore the term “ART-associated TB” has been used to include unmasking IRIS as well as non-IRIS TB diagnosed after ART initiation [4].

A clinically helpful framework for TB-IRIS is to classify each form by the patient population at risk for its development after ART-initiation—paradoxical TB-IRIS is seen in patients with active TB infection undergoing treatment, and unmasking TB-IRIS is seen in patients with occult or subclinical TB that generally has not been diagnosed. CNS-TB-IRIS is seen in patients with neuro-invasive TB and, while technically falling into one of the prior categories, is clinically and pathologically a unique entity with differing immune characteristics and treatment guidelines. In this review we will detail the current state of research on each form of TB-IRIS and describe the gaps in understanding that may serve as opportunities for future study. While TB-IRIS may occur in settings outside of HIV co-infection (for example, with a decrease in immune suppressive medications related to transplantation), the focus of this review relates to HIV [9].

2. CNS-TB-IRIS

Given the physical and immunologic peculiarities of the central nervous system, paradoxical IRIS in the setting of CNS TB requires specific considerations in diagnosis and management. CNS TB-IRIS is common, occurring in nearly half of TB meningitis (TBM) cases in some cohorts [10], and representing the most common etiology of neurological deterioration after ART initiation [11]. However, despite making up about 10% of all TB-IRIS [12], neurological manifestations contribute to the vast majority of TB-IRIS mortality [13][14]. The prognosis of CNS-TB-IRIS is poor with studies showing mortality in 13–30% of cases and disability in an additional 30% [10][12]. Of note, despite paradoxical reactions also being common in HIV-negative TBM, these non-IRIS paradoxical reactions do not adversely impact mortality [15], and therefore parallels between these entities should be made cautiously.

2.1. Clinical Features and Diagnosis of CNS-TB-IRIS

As with all paradoxical TB-IRIS, CNS-TB-IRIS is diagnosed when symptoms of CNS-TB recur after ART-initiation after initially improving on ATT (Figure 1) [4]. Symptoms reappear a median of 14 days after ART initiation [10][12]. CNS TB-IRIS can include all forms of CNS TB—most prominently meningitis, but also intracranial tuberculoma [16], brain abscess [17][18], spinal epidural abscess, and radiculomyelitis [10][12]. The most common symptoms are headache, neck stiffness, confusion and new-onset seizures [10][12]; paraparesis, disconjugate eye movements, aphasia, and decreased vision are also reported [10][15]. Systemic signs of IRIS and TB, such as lymphadenopathy, are also instructive [15]. Inflammation in the CSF typically coincides with symptoms, improving initially during ATT, but then returning to the range at initial presentation; specific thresholds of leukocytes, protein, or glucose have not been established [10][12]. Neutrophils are often predominant at IRIS onset [10][15].

Head and spine imaging are also important for diagnosis as radiologic worsening is itself sufficient for diagnosis of IRIS in some situations [4], and significant hydrocephalus, which is often present in CNS-TB-IRIS, should trigger intervention [15]. Tuberculomas are the most common imaging finding in CNS-TB-IRIS, occurring in 52% of cases in one series, often alongside meningitis [12]. They are generally supratentorial, moderately sized (median 11 mm), and multiple in half of

cases, usually with associated edema, but rarely with mass effect [16]. The presence of multiple lesions and perilesional edema is more common in patients with IRIS than at initial TBM presentation [16]. Presentations localizing to the spinal cord should trigger spine imaging to diagnose radiculomyelitis or epidural abscess [10][12].

While neurologic worsening after ART-initiation in a patient being treated for TBM is strongly indicative of CNS-TB-IRIS, several other conditions should be considered. When CSF culture or molecular diagnostics are positive, it is important to rule out drug-resistant TB, which can occur in more than 10% of TBM cases and is associated with poor outcome [19]. Cryptococcal meningitis, toxoplasmosis, CMV encephalitis, HIV encephalopathy or progressive multi-focal leukoencephalopathy may be present as co-infections with TBM and may be unmasked due to ART [11][12].

2.2. Pathogenesis of CNS-TB-IRIS

Although the immunopathogensis of TB-IRIS in the CNS is likely to mirror that of IRIS outside of the CNS, there are important differences. Many TBM-IRIS associated cytokines, chemokines, and mediators involved in neutrophil response or inflammasome activation are found in the CSF of TBM-IRIS patients in high concentrations, but blood concentrations do not differ significantly between TBM patients with and without IRIS, suggesting a highly compartmentalized inflammatory response [20]. Despite this divergence in apparent inflammatory response, transcriptional profiling has shown expression of similar genes in the blood and CSF [21], thus gene expression does not explain the difference between CNS and peripheral immune responses. Transcripts associated with neutrophil response and both canonical and non-canonical inflammasomes are found at higher concentrations in the blood of patients with TBM-IRIS than in TBM patients without IRIS. S100 A8/A9 (unlike other inflammatory mediators) is elevated in TBM-IRIS even after controlling for baseline culture positivity, which is an independent risk factor for the development of TBM-IRIS [21][20][10].

This understanding of the immunopathology of TBM-IRIS has encouraged efforts to better predict which TBM patients will go on to develop IRIS. As in extra-meningeal TB-IRIS, high viral load and low CD4 T cell count at initial presentation remain risk factors. Further, at TBM diagnosis, increased CSF neutrophil counts (AUC 0.72, 95% CI 0.54–0.90) and CSF culture-positivity (RR 9.3, 95%CI 1.4–62.2) predict future development of paradoxical TBM-IRIS [10]. One model also found high CSF TNF-α and low IFN-γ at TBM diagnosis to be predictive (AUC 0.91, 95%CI 0.53–0.99) of CNS-TB-IRIS [10]. Marais et al. have also used transcriptional analysis to predict IRIS development in TBM, with specific elevation in transcripts associated with neutrophil activation, especially matrix metalloproteinases [21]. These predictors have yet to be validated but show promise in future efforts to tailor both ART timing and immunomodulatory therapies to those patients at most risk of CNS-TB-IRIS.

2.3. Prevention of CNS-TB-IRIS

Protocols for prevention of IRIS are where TBM-IRIS differs most from other forms of TB-IRIS. Unlike in extra-meningeal TB, the high morbidity and mortality of CNS-TB-IRIS makes the risk of IRIS related to early ART initiation higher than the risk of developing additional infections related to delaying ART. The American Thoracic Society and Centers for Disease Control recommend delaying ART initiation until 8 weeks after ATT initiation [22], and other expert opinions recommend at least waiting several weeks from ATT initiation, irrespective of CD4 count [23]. Randomized, controlled trial evidence for this recommendation is provided by a Vietnamese study that showed initiating ART within one week was associated with a significant increase in grade 4 adverse events [24]. U.S. CDC guidelines also recommend 8 weeks of adjunctive corticosteroids with ATT based on a Cochrane metanalysis demonstrating reduced mortality when adding corticosteroids (RR 0.75, 95% CI 0.65 to 0.87) [25]. The rationale for adjunctive steroids is the dampening of pathologic immune responses, of which IRIS is one. This review, however, included only one study with HIV-positive patients (n = 98), and therefore was not able to definitively conclude whether mortality was improved in this subpopulation (RR 0.90, 95%CI 0.67 to 1.20), or to assess incidence of IRIS [25]. There is concern that corticosteroids may in fact lead to poor outcomes in TBM in persons with HIV and an ongoing clinical trial will provide a more definitive answer this question (NCT03092817). Several trials are currently underway to assess intensified antitubercular therapy. Given the association between inadequate mycobacterial killing and TBM-IRIS, these regimens may have an impact on IRIS prevention although whether they will improve TBM outcomes (their goal), let alone prevent IRIS, is unclear [26]. One trial of intensified ATT in TBM published thus far did not improve outcomes overall or in HIV infected subjects specifically—IRIS was not specifically reported on [27].

2.4. Management of CNS-TB-IRIS

While many immunomodulating therapies have been tried with some success in treating CNS-TB-IRIS once it has developed, high-quality evidence is lacking. In fact, many therapeutic trials for TB-IRIS specifically exclude patients with CNS-TB IRIS [28][29]. In one observational study, 18 of 21 patients receiving corticosteroids for CNS-TB-IRIS showed initial

improvement (median 10 days after administration) [12]. Prednisone (1.5mg/kg/day) did not prevent TBM-IRIS in a non-controlled cohort of 34 TBM patients, and dose-increase or restarting of prednisone at IRIS diagnosis decreased the concentration of only two inflammatory mediators (G-CSF, IL-37), while other markers of inflammation remained elevated from ART initiation [20]. This previously-noted finding of limited CNS impact of corticosteroids [30] is in contrast to non-CNS TB-IRIS, where the peripheral immune response is modulated by corticosteroid administration [31][32]. This differential corticosteroid response suggests that more potent or focused immunomodulating therapy might be necessary for TBM-IRIS, whether due to differences in the immune response to CNS TB, or to challenges in reaching adequate CSF concentrations. Several case reports have reported success treating severe cases of CNS-TB-IRIS with TNF-α inhibitors such as infliximab and adalimumab, generally after failure of corticosteroids [[33][34][35][36]. Thalidomide has been used with some effect for treatment of otherwise intractable intracranial tuberculomas [37][38]. However, given thalidomide's teratogenicity, and the early stoppage of a randomized trial in pediatric TBM due to adverse events in the Thalidomide group [39], it should be reserved for severe cases that are refractory to corticosteroids [40][41].

3. Conclusions and Future Directions

TB-IRIS in all forms causes significant morbidity and mortality in persons with HIV/TB coinfection and requires special focus given its partially iatrogenic nature. While significant strides have been made recently, both in the realms of immunology to better understand pathogenesis, and in clinical trials to better optimize prevention and treatment strategies, we are still lacking the knowledge we need to avoid poor outcomes of TB-IRIS—particularly in IRIS related to TBM. As the arsenal of targeted immunosuppressive medications expands, there is newfound opportunity to target our treatments of TB-IRIS to its known immunologic mediators, such as IL-6 or the inflammasome. This will require continued research to better characterize the immune response, as well as rigorous trials to demonstrate improved efficacy and decreased side effects compared to corticosteroids.

Unmasking TB-IRIS remains incompletely described and its prevention will require improved TB detection at ART initiation. As availability of ART and implementation of HIV test and treat continues to increase, ability to rapidly rule out TB coinfection is important. Continued research to identify IRIS biomarkers is of particular importance in unmasking IRIS given its diagnostic challenges.

TB-IRIS in the CNS must be a priority for further research given its high mortality. CSF laboratory tests have been shown to predict TBM-IRIS development, which opens an avenue for targeting advanced immunosuppressants or intensified TB treatment to those at highest risk, but such approaches require clinical trials. Given the localized disease characteristic of CNS-TB-IRIS, it is possible that unique immune-targeted therapies might be beneficial for CNS-TB-IRIS compared to disease outside of the nervous system.

References

1. WHO|Global Tuberculosis Report 2019. Available online: http://www.who.int/tb/publications/global_report/en/ (accessed on 5 June 2020).
2. Bell, L.C.K.; Noursadeghi, M. Pathogenesis of HIV-1 and Mycobacterium tuberculosis co-infection. Nat. Rev. Microbiol. 2018, 16, 80–90.
3. Suthar, A.B.; Lawn, S.D.; del Amo, J.; Getahun, H.; Dye, C.; Sculier, D.; Sterling, T.R.; Chaisson, R.E.; Williams, B.G.; Harries, A.D.; et al. Antiretroviral Therapy for Prevention of Tuberculosis in Adults with HIV: A Systematic Review and Meta-Analysis. PLoS Med. 2012, 9, e1001270.
4. Meintjes, G.; Lawn, S.D.; Scano, F.; Maartens, G.; French, M.A.; Worodria, W.; Elliott, J.H.; Murdoch, D.; Wilkinson, R.J.; Seyler, C.; et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: Case definitions for use in resource-limited settings. Lancet Infect. Dis. 2008, 8, 516–523.
5. Narita, M.; Ashkin, D.; Hollender, E.S.; Pitchenik, A.E. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. Am. J. Respir. Crit. Care Med. 1998, 158, 157–161.
6. French, M.A.; Price, P.; Stone, S.F. Immune restoration disease after antiretroviral therapy. Aids Lond. Engl. 2004, 18, 1615–1627.
7. Shelburne, S.A.; Montes, M.; Hamill, R.J. Immune reconstitution inflammatory syndrome: More answers, more questions. J. Antimicrob. Chemother. 2006, 57, 167–170.
8. Colebunders, R.; John, L.; Huyst, V.; Kambugu, A.; Scano, F.; Lynen, L. Tuberculosis immune reconstitution inflammatory syndrome in countries with limited resources. Int. J. Tuberc. Lung Dis. Off. J. Int. Union Tuberc. Lung Dis.

2006, 10, 946–953.

9. Iglesias, J.; Ledesma, K.J.; Couto, P.J.; Liu, J. Immune Reconstitution Inflammatory Syndrome Occurring in a Kidney Transplant Patient with Extrapulmonary Tuberculosis. Case Rep. Transpl. 2017, 2017, 6290987.
10. Török, M.E.; Yen, N.T.B.; Chau, T.T.H.; Mai, N.T.H.; Phu, N.H.; Mai, P.P.; Dung, N.T.; Chau, N.V.V.; Bang, N.D.; Tien, N.A.; et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2011, 52, 1374–1383.
11. ASSELMAN, V.; THIENEMANN, F.; PEPPER, D.J.; BOULLE, A.; WILKINSON, R.J.; MEINTJES, G.; MARAIS, S. Central Nervous System Disorders after Starting Antiretroviral Therapy in South Africa. AIDS Lond. Engl. 2010, 24.
12. Pepper, D.J.; Marais, S.; Maartens, G.; Rebe, K.; Morroni, C.; Rangaka, M.X.; Oni, T.; Wilkinson, R.J.; Meintjes, G. Neurologic manifestations of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome: A case series. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2009, 48, e96–e107.
13. Namale, P.E.; Abdullahi, L.H.; Fine, S.; Kamkuemah, M.; Wilkinson, R.J.; Meintjes, G. Paradoxical TB-IRIS in HIV-infected adults: A systematic review and meta-analysis. Future Microbiol. 2015, 10, 1077–1099.
14. Agarwal, U.; Kumar, A.; Behera, D.; French, M.A.; Price, P. Tuberculosis associated immune reconstitution inflammatory syndrome in patients infected with HIV: Meningitis a potentially life threatening manifestation. Aids Res. 2012, 9, 17.
15. Singh, A.K.; Malhotra, H.S.; Garg, R.K.; Jain, A.; Kumar, N.; Kohli, N.; Verma, R.; Sharma, P.K. Paradoxical reaction in tuberculous meningitis: Presentation, predictors and impact on prognosis. BMC Infect. Dis. 2016, 16, 306.
16. Marais, S.; Scholtz, P.; Pepper, D.J.; Meintjes, G.; Wilkinson, R.J.; Candy, S. Neuroradiological features of the tuberculosis-associated immune reconstitution inflammatory syndrome. Int. J. Tuberc. Lung Dis. Off. J. Int. Union Tuberc. Lung Dis. 2010, 14, 188–196.
17. Lee, C.-H.; Lui, C.-C.; Liu, J.-W. Immune reconstitution syndrome in a patient with AIDS with paradoxically deteriorating brain tuberculoma. AIDS Patient Care STDS 2007, 21, 234–239.
18. Vidal, J.E.; Cimerman, S.; Schiavon Nogueira, R.; Bonasser Filho, F.; Sztajnbok, J.; da Silva, P.R.M.; Lins, D.L.M.; Coelho, J.F.G.S. Paradoxical reaction during treatment of tuberculous brain abscess in a patient with AIDS. Rev. Inst. Med. Trop. Sao Paulo 2003, 45, 177–178.
19. Marais, S.; Pepper, D.J.; Schutz, C.; Wilkinson, R.J.; Meintjes, G. Presentation and outcome of tuberculous meningitis in a high HIV prevalence setting. PLoS ONE 2011, 6, e20077.
20. Marais, S.; Wilkinson, K.A.; Lesosky, M.; Coussens, A.K.; Deffur, A.; Pepper, D.J.; Schutz, C.; Ismail, Z.; Meintjes, G.; Wilkinson, R.J. Neutrophil-associated central nervous system inflammation in tuberculous meningitis immune reconstitution inflammatory syndrome. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2014, 59, 1638–1647.
21. Marais, S.; Lai, R.P.J.; Wilkinson, K.A.; Meintjes, G.; O'Garra, A.; Wilkinson, R.J. Inflammasome Activation Underlying Central Nervous System Deterioration in HIV-Associated Tuberculosis. J. Infect. Dis. 2017, 215, 677–686.
22. Nahid, P.; Dorman, S.E.; Alipanah, N.; Barry, P.M.; Brozek, J.L.; Cattamanchi, A.; Chaisson, L.H.; Chaisson, R.E.; Daley, C.L.; Grzemska, M.; et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2016, 63, e147–e195.
23. Meintjes, G.; Brust, J.C.M.; Nuttall, J.; Maartens, G. Management of active tuberculosis in adults with HIV. Lancet HIV 2019, 6, e463–e474.
24. Masur, H.; Brooks, J.T.; Benson, C.A.; Holmes, K.K.; Pau, A.K.; Kaplan, J.E.; National Institutes of Health; Centers for Disease Control and Prevention. HIV Medicine Association of the Infectious Diseases Society of America Prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Updated Guidelines from the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association of the Infectious Diseases Society of America. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2014, 58, 1308–1311.
25. Prasad, K.; Singh, M.B.; Ryan, H. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst. Rev. 2016, 4, CD002244.
26. Seddon, J.A.; Tugume, L.; Solomons, R.; Prasad, K.; Bahr, N.C. The current global situation for tuberculous meningitis: Epidemiology, diagnostics, treatment and outcomes. Wellcome Open Res. 2019, 4.
27. Heemskerk, A.D.; Bang, N.D.; Mai, N.T.H.; Chau, T.T.H.; Phu, N.H.; Loc, P.P.; Chau, N.V.V.; Hien, T.T.; Dung, N.H.; Lan, N.T.N.; et al. Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis. N. Engl. J. Med. 2016, 374, 124–134.

28. Meintjes, G.; Wilkinson, R.J.; Morroni, C.; Pepper, D.J.; Rebe, K.; Rangaka, M.X.; Oni, T.; Maartens, G. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. Aids Lond. Engl. 2010, 24, 2381–2390.
29. Meintjes, G.; Stek, C.; Blumenthal, L.; Thienemann, F.; Schutz, C.; Buyze, J.; Ravinetto, R.; van Loen, H.; Nair, A.; Jackson, A.; et al. Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS. N. Engl. J. Med. 2018, 379, 1915–1925.
30. Thwaites, G.E.; Nguyen, D.B.; Nguyen, H.D.; Hoang, T.Q.; Do, T.T.O.; Nguyen, T.C.T.; Nguyen, Q.H.; Nguyen, T.T.; Nguyen, N.H.; Nguyen, T.N.L.; et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N. Engl. J. Med. 2004, 351, 1741–1751.
31. Conesa-Botella, A.; Meintjes, G.; Coussens, A.K.; van der Plas, H.; Goliath, R.; Schutz, C.; Moreno-Reyes, R.; Mehta, M.; Martineau, A.R.; Wilkinson, R.J.; et al. Corticosteroid therapy, vitamin D status, and inflammatory cytokine profile in the HIV-tuberculosis immune reconstitution inflammatory syndrome. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2012, 55, 1004–1011.
32. Meintjes, G.; Skolimowska, K.H.; Wilkinson, K.A.; Matthews, K.; Tadokera, R.; Conesa-Botella, A.; Seldon, R.; Rangaka, M.X.; Rebe, K.; Pepper, D.J.; et al. Corticosteroid-modulated immune activation in the tuberculosis immune reconstitution inflammatory syndrome. Am. J. Respir. Crit. Care Med. 2012, 186, 369–377.
33. Blackmore, T.K.; Manning, L.; Taylor, W.J.; Wallis, R.S. Therapeutic use of infliximab in tuberculosis to control severe paradoxical reaction of the brain and lymph nodes. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2008, 47, e83–e85.
34. Lwin, N.; Boyle, M.; Davis, J.S. Adalimumab for Corticosteroid and Infliximab-Resistant Immune Reconstitution Inflammatory Syndrome in the Setting of TB/HIV Coinfection. Open Forum Infect. Dis. 2018, 5.
35. Lee, H.-S.; Lee, Y.; Lee, S.-O.; Choi, S.-H.; Kim, Y.S.; Woo, J.H.; Kim, S.-H. Adalimumab treatment may replace or enhance the activity of steroids in steroid-refractory tuberculous meningitis. J. Infect. Chemother. Off. J. Jpn. Soc. Chemother. 2012, 18, 555–557.
36. Brunel, A.-S.; Reynes, J.; Tuaillon, E.; Rubbo, P.-A.; Lortholary, O.; Montes, B.; Le Moing, V.; Makinson, A. Thalidomide for steroid-dependent immune reconstitution inflammatory syndromes during AIDS. AIDS Lond. Engl. 2012, 26, 2110–2112.
37. Schoeman, J.F.; Fieggen, G.; Seller, N.; Mendelson, M.; Hartzenberg, B. Intractable Intracranial Tuberculous Infection Responsive to Thalidomide: Report of Four Cases. J. Child. Neurol. 2016.
38. John, M.; French, M.A. Exacerbation of the inflammatory response to Mycobacterium tuberculosis after antiretroviral therapy. Med. J. Aust. 1998, 169, 473–474.
39. Schoeman, J.F.; Springer, P.; van Rensburg, A.J.; Swanevelder, S.; Hanekom, W.A.; Haslett, P.A.J.; Kaplan, G. Adjunctive thalidomide therapy for childhood tuberculous meningitis: Results of a randomized study. J. Child. Neurol. 2004, 19, 250–257.
40. Marais, S.; Wilkinson, R.J.; Pepper, D.J.; Meintjes, G. Management of patients with the immune reconstitution inflammatory syndrome. Curr. HIV/Aids Rep. 2009, 6, 162–171.
41. Roberts, M.T.M.; Mendelson, M.; Meyer, P.; Carmichael, A.; Lever, A.M.L. The use of thalidomide in the treatment of intracranial tuberculomas in adults: Two case reports. J. Infect. 2003, 47, 251–255.