Use of infliximab to treat paradoxical tuberculous meningitis reactions

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Abstract

We documented dramatic responses to infliximab in four tuberculous meningitis cases with severe paradoxical reactions after effective antibacterial treatment; despite high dose steroids. In every instance, infliximab was used as a last resort after all other options were exhausted, resulting in delayed initiation that may have adversely affected patient outcomes.

Keywords: Tuberculous meningitis, paradoxical reactions, infliximab
Introduction

Tuberculous meningitis frequently results in permanent neurological sequelae (1,2). The characteristic inflammatory exudate at the base of the brain may block cerebrospinal fluid (CSF) flow with resultant hydrocephalus, or cause cerebral ischaemia and stroke secondary to vasculitis (1,2). Mass effects associated with localized inflammation may also compromise critical structures, such as the optic chiasm (3). These effects may occur with natural disease progression or as a paradoxical reaction; generally defined as clinical worsening after initial improvement on appropriate antibacterial treatment.

Tumour necrosis factor (TNFα) is critical for effective host defence against mycobacteria and monoclonal antibodies that inhibit TNFα, such as infliximab, greatly increase tuberculosis vulnerability (4). On the other hand, deterioration of tuberculosis patients after infliximab cessation suggests that TNFα may also contribute to disease pathology (5). The use of infliximab to control paradoxical reactions in a patient with tuberculous meningitis was first demonstrated in 2008 (6). Subsequent case reports support the initial observations,(7-10) but awareness of infliximab benefit in select cases is low and completely overshadowed by the perception of risk. Most clinicians remain highly reluctant to consider infliximab use in any tuberculosis patient.

We present a series of tuberculous meningitis cases with likely paradoxical reactions in whom infliximab was used with good effect. The table provides an overview of the case presentation, treatment, clinical progress and outcome, with a focus on the administration and clinical effect of infliximab.
Case 1

A 36-year old male bus driver who migrated to Australia from India 15 months prior was diagnosed with miliary tuberculosis and cerebral tuberculomas. Sputum, bronchoalveolar lavage (BAL), cerebrospinal fluid (CSF) and blood were all culture negative at the time. He was discharged home on isoniazid, rifampicin, pyrazinamide, ethambutol and oral prednisolone. Interim brain magnetic resonance imaging (MRI) showed improvement of tuberculomas, before readmission 6 weeks later with new onset ataxia and drowsiness. Findings on the repeat MRI included hydrocephalus and cerebritis, with the patient experiencing rapid progression to coma requiring intubation and ventilation.

A brain biopsy was performed and an external ventricular drain inserted. The brain biopsy tested Xpert MTB/Rif® positive with rifampicin resistance detected. Empiric MDR treatment was commenced with moxifloxacin, amikacin, prothionamide and linezolid added, awaiting culture results. Phenotypic drug susceptibility testing (DST) identified resistance to all first-line drugs with additional low level resistance to moxifloxacin; line probe assays identified katG, rpoB and gyrA mutations. First-line treatment, except pyrazinamide, was stopped and the patient continued on high dose moxifloxacin with the addition of bedaquiline and clofazimine. On this regimen the patient slowly improved and became more responsive, before deteriorating a second time with new mid-brain tuberculomas, multiple infarcts and increasing leptomeningeal enhancement on MRI.

In the absence of a clinical response to high dose intravenous (IV) dexamethasone a ‘trial dose’ of infliximab was given. Fever and C-reactive protein (CRP) settled promptly and the patient’s sensorium improved within days, allowing him to be weaned off the ventilator. Symptoms recrudesced 3 weeks later with new parenchymal foci and increased enhancement around existing tuberculomas seen on MRI. A second dose of infliximab
induced another prompt response and the patient continued to make a slow recovery, receiving a total of three monthly doses. Linezolid (after 6 months) and amikacin (after 12 months) were ceased due to bone marrow suppression and sensorineural hearing loss respectively. In total, the patient completed 24 months of treatment and was discharged to a disability home where he lives independently with minimal caregiver help.

**Case 2**

A 32-year old woman (on TB treatment) presented with a 7-day history of bilateral thigh pain and paraesthesia, gait disturbance and urinary retention. Spinal MRI revealed compressive lesions at T5 and T11/12; occurring 4 months after commencing treatment for culture-confirmed miliary tuberculosis; CSF was not assessed at the time. Tuberculosis treatment consisted of isoniazid, rifampicin, pyrazinamide, ethambutol (isoniazid discontinued after documented high-level resistance) and moxifloxacin, with excellent treatment adherence and no vomiting or clinical indication of malabsorption, such as diarrhoea. High dose IV dexamethasone was initiated and an urgent T4-6 and T11-12 laminectomy performed, complicated by dense pachymeningeal adhesions. With new onset faecal incontinence further debulking of the T11/12 lesion was performed, but distressing symptoms persisted.

Histopathology from both lesions showed necrotising granulomas, negative for acid fast bacilli and mycobacterial growth. In the absence of live bacilli or any documented steroid response infliximab was started, with rapid clinical improvement. Full bowel and bladder control, as well as mobility was regained within 2 weeks. In the absence of raised inflammatory markers, serial positron emission tomography (PET) scans were used to track treatment response with significant reduction in glucose uptake at 2 months and no ongoing activity detected at 4 months, when infliximab treatment was stopped.
Case 3

A 53-year old woman visiting from Indonesia presented with paraplegia, faecal incontinence and urinary retention, as well as headache and a third cranial nerve palsy. Extensive intracranial and intraspinal leptomeningeal and pachymeningeal enhancement was demonstrated on MRI. Her CSF grew a fully susceptible strain of *Mycobacterium tuberculosis*. Therapy with isoniazid, rifampicin, pyrazinamide and moxifloxacin together with high-dose steroids led to initial improvement with resolution of headaches and the third nerve palsy, but after seven weeks of treatment and while still on high dose steroids, the patient experienced worsening headaches and new onset vomiting. Repeat MRI demonstrated increased leptomeningeal inflammation with multiple new intracranial and intraspinal tuberculomas (Figures 1 and 2).

Treatment with infliximab resulted in rapid clinical improvement. Fever and headaches briefly recurred before the second monthly dose; with a total of three monthly doses administered. High dose oral steroids were continued for 4 months before slow tapering. Thalidomide and lenalidomide were trialled for longer term inflammatory suppression, but both resulted in an extensive generalised rash and were discontinued. A progress MRI demonstrated significant improvement in the leptomeningeal enhancement and ring enhancing tuberculomas after 6 months of therapy. The patient returned to Indonesia eight months after treatment initiation, having regained muscle strength, but sphincter function remained compromised.
Case 4

A 26-year old male student from India was admitted with cough, weight loss and lethargy. There were multiple lung cavities on chest computed tomography (CT), but he had no neurological signs and a non-contrast CT scan of the brain detected no intracranial pathology. He commenced treatment on standard first-line therapy without corticosteroids. Within days of treatment initiation he developed headache, vomiting and disorientation, with bilateral lower limb weakness and urinary retention. A MRI of the brain and spine demonstrated communicating hydrocephalus with extensive leptomeningeal enhancement involving the spine, as well as multilevel spondylodiscitis with paravertebral abscesses. A lumbar drain was inserted and high dose IV dexamethasone commenced, the rifampicin dose was increased to 900 mg/day and levofloxacin 750 mg/day added. *M. tuberculosis* grown from sputum was subsequently shown to be fully drug susceptible.

Six weeks later, while still on IV dexamethasone, the patient developed new fever, worsening leg weakness and diplopia. MRI of the brain and spine demonstrated increased basal meningeal enhancement, a new left occipital tuberculoma and evidence of compressive myelopathy with progression of the spondylodiscitis. Fever and neurological symptoms improved rapidly after a dose of infliximab. Following symptom recrudescence repeat infliximab doses were given 3, 7 and 17 weeks later, each time followed by prompt improvement. Repeat MRI at 6 months demonstrated resolution of the meningitis, hydrocephalus, tuberculomas and spondylodiscitis with improvement of the paravertebral abscesses; now regarded as too small for drainage. The antibacterial treatment was rationalized to rifampicin and isoniazid with a plan to treat for 12 months in total.
Discussion

All four cases experienced clinical deterioration despite adequate antibacterial treatment and high dose corticosteroids. In every instance infliximab therapy was followed by rapid clinical improvement; no adverse effects were reported. The pronounced and consistent temporal association in clinical improvement, as well as MRI and/or PET changes suggest a strong therapeutic effect. Our findings support observations that TNFα is a key driver of inflammation in TB meningitis,(11) and is consistent with the therapeutic effect observed in previous reports, (6-10) including those using other TNFα inhibitors, such as adalimumab (12) and thalidomide (3). Monoclonal antibodies do not usually cross the blood brain barrier, but may do so in the presence of meningeal inflammation and barrier disruption. In rats with hepatic encephalopathy infliximab significantly reduced neuroinflammation, as demonstrated on immunohistochemistry (13). In all reported cases, infliximab was only considered after other treatment options were exhausted, but earlier commencement may have prevented some of the invasive procedures and permanent sequelae. It should be emphasized that anti-TNFα treatment should only be contemplated in the presence of effective antibacterial therapy with adequate CSF penetration (14).

The optimal timing and duration of anti-TNFα treatment, as well as the value of corticosteroid co-administration remains unclear. Symptomatic improvement, inflammatory markers (if raised to begin with) and MRI or PET changes may guide treatment duration; 3-4 doses of infliximab led to significant and durable clinical improvement in all patients. Although optimal dosing and timing of delivery remains uncertain, a rational approach may be to give 5mg/kg at 0, 2, and 6 weeks (similar to induction dosing recommended for patients with active psoriatic arthritis), with consideration of additional doses at 10-14 weeks guided by the treatment response. This is based on three monthly doses provided in the first description of infliximab use in TB meningitis (6) and the fact that our patients experienced 'breakthrough
symptoms’ before the second monthly dose. Therapeutic drug monitoring would be useful to inform dosing schedules (15), but is rarely available and was not performed in our patients. The added value of high dose corticosteroids is uncertain and require further evaluation; in reported cases deterioration occurred under ‘steroid cover’.

Randomized controlled trials to assess the benefit of infliximab use in tuberculous meningitis, in conjunction with effective antibacterial treatment, would be highly informative and might be considered in the following situations: 1) in immune competent (HIV uninfected) patients with paradoxical reactions, 2) in TB/HIV co-infected patients who experience immune reconstitution inflammatory syndrome (IRIS) affecting the central nervous system and 3) as part of routine care to prevent severe and irreversible sequelae. Multicentre recruitment using standardized methods is preferred (16), although the numbers required to detect a pronounced therapeutic effect, which is the key clinical need, would be relatively small.
References

1. Marais S, Thwaites G, Schoeman J et al. Tuberculosis Meningitis: defining a uniform case definition for use in clinical research. Lancet Infect Dis 2010; 10: 803-12

2. Wilkinson RJ, Rohlwink U, Misra UK et al. Tuberculous meningitis. Nat Rev Neurol 2017; 13: 581–98

3. Schoeman JF, Andronikos S, Stefan DC, Freeman N, van Toorn R. Tuberculous meningitis-related optic neuritis: Recovery of vision with thalidomide in 4 consecutive cases. Journal of Child Neurology 2010; 25: 822 – 8

4. Keane J, Gershon S, Wise RP et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001; 345: 1098–104

5. Vidal CG, Fernandez SR, Lacasa JM et al. Paradoxical response to antituberculous therapy in infliximab-treated patients with disseminated tuberculosis. Clin Infect Dis 2005; 40: 756-9

6. Blackmore T, Manning L, Taylor W, Wallis R. Therapeutic use of infliximab in tuberculosis to control severe paradoxical reaction of the brain and lymph nodes. Clin Inf Dis 2008; 47: 83-5

7. Jorges J-H, Gracielia C, Pablo A-P, Luis S-HJ. A life-threatening central nervous system-tuberculosis inflammatory reaction non responsive to corticosteroids and successfully controlled by infliximab in a young patient with a variant of juvenile idiopathic arthritis. J Clin Rheumatol 2012;18:189-191

8. Molton JS, Huggan PJ, Archuleta S. Infliximab therapy in two cases of severe neurotuberculosis paradoxical reaction. Med J Aust 2015; 202: 156–157

9. Hsu DC, Faldetta KF, Pei L et. al. A paradoxical treatment for a paradoxical reaction: infliximab use in three cases of mycobacterial IRIS. Clin Infect Dis 2016; 62: 258–61

10. Abo Y, Curtis N, Butters C, Rozen TH, Marais BJ, Gwee A. Successful treatment of a severe vision-threatening paradoxical tuberculous reaction with infliximab: first pediatric use. Ped Infect Dis J 2020; 39: e42-e45

11. Donald PR, Schoeman JF, N. Beyers ED, Nel ED, Carlini SM, Olsen KD, McCracken GH. Concentrations of Interferon γ, Tumor Necrosis Factor α, and Interleukin-1β in the cerebrospinal fluid of children treated for tuberculous meningitis, Clin Infect Dis 1995: 21: 924–92

12. Wallis RS, van Vuuren C, Potgieter S. Adalimumab treatment of life-threatening tuberculosis. Clin Infect. Dis 2009; 48, 1429–32

13. Dadsetan S, Balzano T, Forteza J et al. Infliximab reduces peripheral inflammation, neuroinflammation, and extracellular GABA in the cerebellum and improves learning and motor
14. Huynh J, Marais BJ. Multidrug resistant tuberculosis infection and disease in children: a review of new and repurposed drugs. Ther Adv Infect Dis 2019; 19; 6

15. Syversen SW, Goll GL, Jørgensen KK et al. Therapeutic drug monitoring of infliximab compared to standard clinical treatment with infliximab: study protocol for a randomised, controlled, open, parallel-group, phase IV study (the NOR-DRUM study). Trials 2020; 21: 13

16. Marais BJ, Heemskerk AD, Marais S et al. Standardized Methods for Enhanced Quality and Comparability of Tuberculous Meningitis studies. Clin Infect Dis 2017; 64: 501-9
### Table. Tuberculous meningitis cases with paradoxical reactions treated with infliximab

| Case | Diagnosis at presentation | Site of paradoxical reaction | TB treatment regimen | Other treatment before and after infliximab | Infliximab dose | Outcome |
|------|-------------------------|-------------------------------|----------------------|----------------------------------------|----------------|---------|
| Case 1 | Flinders Hospital, Adelaide 36yrs, male HIV uninfected India* | Miliary TB with TBM | Multiple brain tuberculomas and obstructed CSF flow with raised ICP | **Before**: High dose steroids** for 3 months  
**After**: High dose steroids for 4 months; tapered over 2 months | 10mg/kg monthly x3 | Rapid fever resolution with CRP decline; improved sensorium allowing weaning off the ventilator within days  
Long term - mild cognitive deficit, require assistance with activities of daily living |
| Case 2 | Concord Hospital, Sydney 32yrs, female HIV uninfected China** | Miliary TB with TBM | Multiple spinal tuberculomas with oedema and local mass effect | **Before**: High dose steroids for 2 months; decompressive spinal surgery  
**After**: High dose steroids for 2 months; tapered over 1 month | 5mg/kg 0, 2, 6 and 14 weeks | Rapid restoration of bladder function (2 weeks) and mobility (3-4 weeks)  
Long term - full neurological recovery |
| Case 3 | Royal North Shore Hospital, Sydney 55yrs, female HIV uninfected Indonesia*** | TBM and necrotic lymphadenitis | Multiple brain and spinal cord tuberculomas with cauda equina syndrome | **Before**: High dose steroids for 2 months  
**After**: High dose steroids for 4 months; failed trial of | 5mg/kg monthly x3 | Rapid resolution of fever and meningism; improvement in lower limb power  
Long term – incomplete recovery with compromised sphincter function at discharge; regained mobility with ongoing improvement in lower limb power |
| Case 4 | PTB with CNS and bone involvement | Multiple brain and spinal tuberculomas with raised ICP, compressive spinal myelopathy and cold abscesses | Empiric HRZE, then HR(900mg)Z + lfx |
|-------|----------------------------------|-------------------------------------------------|------------------------------------|
| Before: High dose steroids for 6 weeks with unsuccessful weaning | After: High dose steroids for 2 months; tapered over 1 month | 10 mg/kg (0, 3 weeks) 5 mg/kg (7, 17 weeks) | Rapid resolution of fever and neurological improvement (reduced pressure effects) Long term – regained sphincter function and mobility with ongoing improvement on rehabilitation |

ICP – intracranial pressure; CNS – central nervous system; HIV - human immunodeficiency virus; TB - tuberculosis; PTB – pulmonary TB; TBM - TB meningitis; H – isoniazid; R - rifampicin; Z - pyrazinamide; E – ethambutol; mfx – moxifloxacin; lfx – levofloxacin; amk - amikacin; lzd – linezolid; pto – prothionamide; bdq – edaquinile; cfz – clofazimine; yrs - years

#Country of origin

##High dose steroids included intravenous dexamethasone (4-8mg 3-4x/day) and/or oral prednisone (1-2mg/kg/day - maximum 60mg/day)

*after identification of pan-resistance to all first-line drugs, including high level isoniazid and low level moxifloxacin resistance

**linezolid (6 months) and amikacin (12 months) stopped after demonstrated toxicity

***isoniazid replaced by moxifloxacin given high level isoniazid mono resistance
Figure 1. T1 weighted post gadolinium MRI brain images demonstrating evolution of brain tuberculomas in Case 3; pre- and post-infliximab use

MRI brain at a) time of presentation, b) week 7 post commencement of TB therapy with formation of multiple tuberculomas (pre-infliximab) and c) week 21 post commencement of TB therapy and after 3 doses of infliximab, demonstrating complete resolution of brain tuberculomas.

Figure 2. T1 weighted post gadolinium MRI brain images demonstrating evolution of spinal tuberculomas in Case 3; pre- and post-infliximab use

MRI spine at a) time of presentation, b) week 7 post commencement of TB therapy with formation of spinal cord tuberculoma (pre-infliximab) and c) week 21 post commencement of TB therapy and after 3 doses of infliximab, demonstrating incomplete resolution of spinal cord tuberculoma.
Figure 1b
Figure 1c
