European Review for Medical and Pharmacological Sciences 2010; 14: 845-853

Management of central nervous system tuberculosis in children: light and shade

D. BUONSENSO, D. SERRANTI, P. VALENTINI

Department of Pediatrics, Catholic University of the Sacred Heart, Rome (Italy)

Abstract. – *Background:* **Pediatric tuberculosis of the central nervous system (CNS-TB) is a severe form of extrapulmonary TB. It is most common in children between 6 months and 4 years of age. CNS-TB can present as meningitis and/or tuberculoma. In both situations, brain damage results from a cytokine-mediated inflammatory response, which causes vasculitis, obstructive hydrocephalus and cranial nerve palsy. Tumor necrosis factor alpha (TNF-α) is an important cytokine in this response.**

The prognosis of tuberculous meningitis (TBM) correlates most closely with the clinical stage of illness at the time treatment is started. Most patients in the 1st stage have a good outcome, whereas the management of patients in the 2nd and 3rd stage is still a clinical challenge, and the few patients who survive have permanent severe disabilities.

Due to the important role of inflammation in CNS-TB pathogenesis, corticosteroids are routinely used in TBM or tuberculomas, in order to reduce death and disabling residual neurological deficits among survivors. Nevertheless, not all patients show a good response to standard anti-inflammatory treatment. Thalidomide is a drug with pleiotropic effects: it appears to down-regulate production of TNF-α and other proinflammatory cytokines. Due to its anti-inflammatory effects, thalidomide has been evaluated as an adjunctive drug in the management of difficult-to-treat CNS-TB.

Materials and Methods: **A literature review was carried out based on MEDLINE/pubmed database (1997/2010) searching for the following descriptors: corticosteroids and tuberculous meningitis (limits: review, all child); thalidomide and tuberculosis treatment; and tuberculous meningitis; and CNS-TB; and brain abscess; and TB clinical trial.**

Aims: **Literature review on the use of corticosteroids and thalidomide in the treatment of CNS-TB.**

Results: **The Cochrane review for randomized-controlled trials evaluating the use of steroids in TBM showed significantly reduced overall mortality, reduced death and severe residual disability in children. Regarding the use of thalidomide, a randomized controlled trial published in 2004 do not support the use of adjunctive high-dose thalidomide therapy in the treatment of TBM in children, but results from four case reports, one clinical trial and one placebo-controlled trial suggest the use of thalidomide in CNS-TB not responding to standard therapy.**

Conclusion: **"Adjuvant" treatment with dexamethasone improves survival in patients with TBM but probably does not prevent disability. Thalidomide should not be used for the routine treatment, but it may be helpful as a "salvage therapy" in patients with TBM and tuberculomas not responding to anti-TB drugs and high dose corticosteroids. More studies should evaluate its not completely conclusive role.**

Key Words:

Tuberculous meningitis, Children, Therapy.

Introduction

Tuberculosis of the Central Nervous System (CNS-TB) is the most severe extrapulmonary complication of TB, with high morbidity and mortality rates. It results from hematogenous spread of primary or post-primary pulmonary disease or from the rupture of a subependymal tubercle into the subarachnoid space.

Three clinical stages of CNS-TB have been described. The 1st stage (mild cases), which typically lasts 1-2 weeks, is characterized by non-specific symptoms, such as fever, headache, irritability, drowsiness, and malaise. The 2nd stage (moderately advanced cases) is characterized by altered sensorium, lethargy, nuchal rigidity, seizures, positive Kernig or Brudzinski signs, hypertonia, vomiting, cranial nerve palsies, and other focal neurologic signs. In the 3rd stage (severe

Corresponding Author: Piero Valentini, MD; e-mail: pvalentini@rm.unicatt.it

cases) there is a deterioration of vital signs due to the development of hydrocephalus, increased intracranial pressure (ICP), vasculitis, coma, hemiplegia or paraplegia, hypertension, decerebrate posturing, and eventually death.

In clinical practice two different types of CNS involvement may develop: tuberculous meningitis (TBM), or meningoencephalitis, and tuberculoma.

TBM is the most serious extra-pulmonary manifestation of TB. It is typically most pronounced over the basal meninges. Because of the proximity of the circle of Willis, a vasculitic inflammation of key vessels also arises, with further cerebral injury secondary to infarction. In children, TBM is associated with about 50% mortality, and most of the survivors have permanent neurologic sequelae, such as severe disability. 50% of all patients are younger than 2 years old. TBM starts with non-specific symptoms and is often diagnosed when brain damage is already occurred. The disease is diagnosed clinically, with confirmation by microscopy, culture of cerebrospinal fluid (CSF), or polymerase chain reaction test.

Disability in TBM is multifactorial. Important causes of disability are persistent or progressive hydrocephalus, multiple cranial nerve involvement, vasculitis leading to cerebral infarcts and stroke, hemiplegia or paraplegia.

Earlier diagnosis improves outcome significantly. However, outcome is not solely linked to time of diagnosis and beginning of treatment. The introduction of newer agents did not lead to further dramatic improvements in survival and the mortality for stage 3 disease remains approximately 50%[1].

Ethnicity and stage of disease, headache, convulsions, motor function, brainstem dysfunction and cerebral infarctions are all factors independently associated with poor outcome[2].

Tuberculomas are an uncommon presentation of CNS-TB in children, occurring in 5% of children who have CNS-TB. They appear as rimenhancing lesions ranging from 1 to 5 cm. Clinically these lesions present with signs of raised ICP, seizures and/or localizing signs. The diagnosis of tuberculomas is confirmed by cranial computed tomography (CT) or magnetic resonance imaging (MRI).

Treating CNS-TB is still a clinical challenge. Both TBM and tuberculomas are notoriously difficult to treat, often responding poorly to conventional TB treatment.

CNS-TB need to be treated by two different points of view: both the microbiological and the inflammatory ones.

In fact, anti-TB therapy alone does not improve outcome significantly despite reductions in bacillary load. Rather, after initiation of therapy, patients often progress to severe neurologic signs and death. This may be due to antibiotic killing of mycobacteria and release of cell wall products which further increases the inflammation in the CNS, resulting in damage of the vessels accompanied by infarcts, brain edema, and necrosis. For this reason, in order to reduce the inflammation accompanying TBM or tuberculomas, standard anti-TB therapy usually includes antiinflammatory treatment ("adjuvant therapy"), such as corticosteroids.

Without treatment, people with TBM die. Streptomycin (STP) reduces the case-fatality rate to 63%[3]. Newer antiTB drugs – isoniazid (INH), rifampicin (RFM), pyrazinamide (PZD) and ethambutol (ETM) – are associated with better survival, but mortality remains high.

The optimal drug regimen and duration of TBM are not clearly established. However, treatment courses of 9 to 12 months are often used. Children infected with multidrug-resistent TB are often treated for 12 to 18 months.

INH and RFM are the key components of the regimen. INH penetrates the CSF freely and has potent early bactericidal activity[4].

RFM penetrates the CSF less well (10-20%), but easily achieves the minimum inhibitory concentrations in mycobacterium cells. In fact, the high mortality from RFM resistant TB has confirmed its central role in the treatment of CNS disease[5].

PZD is well absorbed orally and achieves high concentrations in the CSF.

INH, RFM and PZD are considered mandatory at the beginning of TBM treatment, when appropriately and adequately administered.

There are no data from controlled trials to guide choice of the fourth drug. Regarding to the fourth drug, most authorities recommend either STP or ETM, although neither penetrates the CSF well in the absence of inflammation and both can produce significant adverse reactions. Some centers advocate ethionamide, which penetrates healthy and inflamed meninges but it can cause severe nausea. The fluoroquinolones may represent an effective fourth agent, although data concerning their use are limited and their prolonged use is not advised for children[6].

Table I. CNS penetrance and toxicity of the main anti-tuberculous drugs.

Agent	CNS penetrance	Toxicities
Isoniazid	100%	Hepatitis, peripheral neuropathy, nausea
Rifampin	10-20%	Hepatitis, nausea
Pyrazinamide	100%	Gut, rash
Ethambutol	Minimal	Optic neuritis, although at the standard dose of 20 mg/kg the incidence is less than 3%
Streptomycin	Minimal	Ototoxicity, nephrotoxicity; resistance relatively common worldwide
Ethionamide	100%	Hepatotoxicity, severe nausea and vomiting
Levofloxacin	16-20	Arthropaty, nausea and bloating

Adapted from Cruz and Starke, Pediatric tuberculosis, Pediatr Rev 2010; 31: 13-26.

A systematic review[7] and meta-analysis concluded that six months of treatment were probably sufficient for TBM, even though some Authorities[8] recommend 12 months treatment, prompted by the uncertainty of undetected drug resistance and patient compliance.

Hepatic toxicity is the commonest serious drug-related event. Liver enzyme abnormalities may resolve spontaneously or with INH dose reduction, followed by a gradual reintroduction after liver function recovery[9].

INH should be stopped if transaminases rise above three times normal range, because of the risk of developing fulminant hepatitis, and substituted by alternative drugs[10].

Table I shows the most important pharmacological characteristics and adverse effects of the main anti-TB drugs.

Corticosteroids have been using for treatment of TBM since the 1950s. Their use seems to be logical in order to suppress the unwanted inflammatory events arising in response to infection with *Mycobacterium tuberculosis*. In TBM there are a lot of well-known damaging host factors implicated in clinical deterioration: local inflammation, blood brain barrier (BBB) disruption, increased ICP, central nervous injury due to reactive oxygen species (ROS) and vascular damage.

Glucocorticoids are potent anti-inflammatory and immunomodulatory agents. They have a number of effects that mitigate these damaging host factors: they diminish transcription of proinflammatory cytokines and chemokines, diminish adhesion molecules expression, diminish cell recruitment, activation and proliferation, decrease CSF matrix metalloproteinase 9 concentrations[11], diminish local inflammation, reduce swelling and congestion of the meninges and ICP, CNS edema and CSF outflow resistance, diminish synthesis of lipolytic and proteolytic enzymes, promote BBB repair[12].

However, steroids also have immunosuppressive effects, and concerns remain that their use might worsen outcome in CNS-TB because of failure of immune response against the organism. Moreover, some Authors have suggested that the reduced inflammation of the meninges, achieved by corticosteroid treatment, could reduce the ability of drugs to seep into the subarachnoid space.

Table II shows treatment schedules for CNS-TB in children, suggested by the British Thoracic Society (BTS), the American Academy of Pediatrics (AAP) and the World Health Organization (WHO).

Table III summarizes the main aspects regarding TBM treatment.

Table II. Treatment schedules for CNS-TB in children.

BTS	AAP	WHO
2 months ISN-RFM-PZD-STP (ETM/STP*) than 10 months ISN-RFM	2 months ISN-RFM-PZD-STP than 10 months ISN-RFM	2 months ISN-RFM-PZD-STP than 14 months ISN-RFM

*If resistance suspected. Adapted from Shingadia and Novelli V. Lancet Infect Dis 2003; 3: 624-632.

Table III. CNS penetrance and toxicity of the main anti-tuberculous drugs.

Drugs	Daily dosage, mg/kg	Twice a week dosage, mg/kg x dose	Maximum dose	Comments
Isoniazid	10-15	20-30	300 mg/daily	9 to 12 months, for drug-susceptible *M. tuberculosis*
Pyrazinamide	30-40	50	2 g	2 mo
Rifampin	10-20	10-20	600 mg	9 to 12 months, for drug-susceptible *M. tuberculosis*
Ethambutol	20-25	50	2,5 g	Given as 4th with initialtherapy untl drug susceptibilitys known, then discontinued
Prednisone	2		60 mg/day	4 to 6 weeks, followed by tapering. Incomplete evidences support its use
Streptomycin	20-40 (intramuscular administration)		1 g	Second-line drug, good alternatives fourth agent in susceptible tuberculosis
Ethionamide	15-20 (intramuscular administration)		1 g	Second-line drug, good alternatives ethambutol, usually used for treatment of drug-resistant tuberculosis

For suspected drug-susceptible TBM, daily treatment with isoniazid, rifampin, pyrazinamide and ethambutol should be used. When susceptibility to all drugs is established, ethambutol can be discontinued.
Adapted from American Academy of Pediatrics (Tuberculosis). In Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. Red Book: 2009 Report of the Commettee on Infectious Diseases. 28° ed. Elk Grove Village, IL American Acedemy of Pediatrics; 2009: 688,689,692.

Nevertheless, both the paradoxical enlargement of existing lesions and the progressive meningeal inflammation during antimicrobial and corticosteroid therapy are a well recognized phenomenon, overall in stage III CNS-TB.

In these circumstances a more aggressive anti-inflammatory therapy has been tried and some reports have described the treatment of difficult-to-treat TBM by use of thalidomide, a potent TNF-α inhibitor.

In this article, we made a literature review on the use of corticosteroids and thalidomide in the treatment of CNS-TB.

Materials and Methods

A literature review has been performed from January 1997 to April 2010, using the MEDLINE/pubmed database and the following descriptors: corticosteroids *and* tuberculous meningitis (limits: review, all child), 19 hits; thalidomide *and* tuberculosis treatment (48hits); *and* tuberculous meningitis (11 hits); *and* CNS-TB (11 hits); *and* brain abscess (3 hits); *and* TB clinical trial (17 hits). Altogether we obtained 68 hits, of which 44 since 1997, 24 of that were relevant. As to the type, our study includes: one randomized controlled trial, which enrolled 47 children; four case reports, regarding six children and two adults; one clinical trial evaluating 15 children; twelve reviews; five research studies (Research Support, Non-U.S. Gov't); one placebo-controlled study.

Articles were excluded if: publications did not primarily evaluate the use of thalidomide or corticosteroids in CNS-TB; they were letters only.

Results

First trials in the 1950s suggested benefits for the use of steroids[13].

Girgis et al.[14] reported the outcome of 160 individuals in a non controlled trial. Patients randomized to steroid treatment showed improved survival, overall among stage 2 and 3 disease.

A further report from the same group[15] confirmed that mortality was dependent on stage of disease and duration of illness at presentation.

Kumarvelu et al[16] reported the results for 47 cases of TBM. The Authors reported improvements for patients with steroids, although no sig-

nificant effects were shown for death or disabling residual deficits.

Schoeman et al[17] reported the effects of prednisolone among 141 children with stage II and III TBM. Steroids resulted in a significant reduction in mortality but, once again, no significant differences were found in motor deficits, blindness or deafness.

Thwaites et al[18] published a randomized, placebo-controlled trial evaluating 545 patients over the age of 14 years with TBM in Vietnam. This trial showed no significant difference for the combined outcome of death or severe neurological disability between cases treated with dexamethasone or placebo. The use of steroids resulted in significantly improved outcome when the analysis was limited to fatality alone. Significantly more adverse events, such as hepatitis, were reported in the placebo group than the patients treated with dexamethasone. No adverse events directly related to steroids treatment were reported.

The use of steroids in TBM has also been addressed by two Cochrane systematic reviews, published in 2000[19] and 2008[20].

These reviews identified seven trials involving 1140 (with 411 deaths) people that evaluated either dexamethasone or prednisolone given in addition to anti-TB drugs. The analyses showed that corticosteroids help reduce the risk of death (RR 0.78, 95% CI 0.67 to 0.91; 1140 participants, 7 trials) or disabling residual neurological deficit (RR 0.82, 95%CI 0.70 to 0.97; 720 participants, 3 trials).

None of the trials reported dissemination of TB owing to a possible immunosuppressive effects of adjuvant steroids.

Adverse events included gastrointestinal bleeding, bacterial and fungal infections, electrolyte disturbances and hyperglycaemia, but they were mild and treatable. Moreover, the results reported by Thwaites et al[18] showed that patients treated with steroids had less hepatitis when taking anti-TB drugs, and this resulted in reduced interruption and changes in antibiotic regimen.

Only one trial evaluated the effects of corticosteroids in HIV-positive people, but results were unclear[21].

The progression of clinical signs and symptoms and pathological lesions of patients with CNS-TB whilst on steroids, is a well-known and widely described phenomenon. Therefore, some investigators looked for different drugs able to decrease CNS inflammation in not-responding CNS-TB.

The use of thalidomide in the treatment of CNS-TB has been suggested after the recognition of the essential role of TNF-α in the pathogenesis of this form of TB.

Thalidomide is a drug with complex anti-inflammatory, immunological and metabolic effects. It affects cytokine production and T lymphocyte proliferation, suppresses TNF-α production and reduces inflammatory response. Thalidomide costimulates T lymphocytes, with greater effect on CD8+ than on CD4+ T cells. This finding is important, since CD8+ T cells have been shown to be contributory to the protective immune response to *Mycobacterium tuberculosis* infection[22].

The immunomodulatory effects of thalidomide were first discovered when it was shown to heal the inflammatory skin lesions of erythema nodosum leprosum in patients with leprosy, maybe due to the reduction in TNF-α circulating levels, mediated by thalidomide[23].

First studies on the use of thalidomide in TBM were conducted in 1997 and 1998. Experiments were performed on a rabbit model of acute mycobacterial CNS infection. Inoculation of live *Mycobacterium bovis Ravenel* (MbR) intracisternally induced leukocytosis, high protein levels, and release of TNF-α into the CSF within 1 day. Histologically, severe meningitis with thickening of the leptomeninges, vasculitis encephalitis were apparent, and mortality was 75% by day 8.

In animals treated with anti-TB antibiotics only, the inflammation and lesions of the brain persisted despite a decrease in mycobacteria; 50% of the rabbits died. When thalidomide treatment was combined with antibiotics, a marked reduction in TNF-α levels, leukocytosis and brain pathology was verified. With this treatment, 100% of the infected rabbits survived, suggesting a role of TNF-α in the pathogenesis of TBM and the potential clinical use for thalidomide in this setting[24,25].

The role of TNF-α as a determinant of mycobacterial pathogenicity in the CNS has been widely studied by Tsenova et al[26].

In the CNS, TNF-α triggers the release of other cytokines, influences transport of compounds into the brain by ''opening'' the blood-brain barrier, correlates with increased levels of interleukin (IL)-6 and protein, as well as low glucose levels. In addition, TNF-α and IL-1b levels are associated with prolonged fever, seizures, spasticity, and death. Moreover, TNF-α affects vascu-

lar endothelium by inducing procoagulant activity, formation of thrombi, and production of nitric oxide synthase, thus causing endarteritis. Occlusions of large or small vessels are the most common reason for cranial nerve palsies, hemiparesis, and paralysis[26].

The same Authors[27] examined whether a new thalidomide analog, immunomodulatory drug 3 (IMiD3), would be effective in reducing morbidity and mortality in an experimental rabbit model of TBM. Intracisternal inoculation of MbR in rabbits induced progressive subacute meningitis characterized by high cerebrospinal leukocytosis, protein concentration, release of TNF-α and mortality by day 28. Treatment with antituberculous drugs in combination with IMiD3 limited pathological neurologic changes and resulted in marked improvement (73%) in survival, with reduced leukocytosis and TNF-α levels in the cerebrospinal fluid (CSF) and plasma. Histologically, the meningeal inflammation was considerably attenuated compared to that of the other treatment groups. These results indicate that IMiD3 may be even more effective than thalidomide[27].

Consequently, a clinical trial[28] on the efficacy, safety and tolerability of thalidomide, an immunomodulatory agent, as adjunctive therapy in children with TBM was carried out. Fifteen children with stage 2 TBM received oral thalidomide for 28 days in a dose-escalating study, in addition to the standard four-drug antituberculosis therapy, corticosteroids, and specific treatment of complications such as raised ICP.

Thalidomide was administered in a dosage of 6 mg/kg/day, 12 mg/kg/day, or 24 mg/kg/day. Levels of TNF-α in the CSF decreased markedly during thalidomide therapy. Clinical outcome and neurologic imaging showed greater improvement than that experienced with controls. Thalidomide appeared safe and well tolerated. The only adverse events possibly related to the drug were transient skin rashes in two patients. These promising results have led the Authors to embark on a randomized, double-blind, placebo-controlled trial of the efficacy of thalidomide in TBM.

Because of the poor clinical and radiological response to anti-TB treatment and steroids, Schoeman et al in 2001[29] reported a study on thalidomide (24 mg/kg/day, total daily dose: 300 mg), added to the standard treatment regimen. Thalidomide therapy was continued for 4 months, during which time the patient made an excellent clinical recovery with no recurrence of symptoms of raised intracranial pressure, apart from moderate residual weakness of the right leg, that, however, resolved with the passage of time.

A successful use of thalidomide has also been reported in a case report published in 2003[30]. The Authors presented two cases of TBM in adults complicated by focal neurological deficits which showed progression whilst on steroids. In case 1 an MRI demonstrated multiple ring-enhancing lesions compressing the optic chiasm, leading to bitemporal hemianopsia. After the introduction of thalidomide the patient showed progressive improvement, demonstrated by both MRI imaging and the resolution of hemianopsia. In case 2, two months into anti-TB treatment with steroids, the patient developed fluctuating right sided paralysis with the MRI demonstrating a large ring-enhancing mass encasing the left internal carotid and middle cerebral arteries. Thalidomide was introduced as an immunomodulatory adjunct and subsequently the patient made a complete neurological recovery.

So the immunomodulatory effects of thalidomide may have a role in the acute and chronic management of TBM complicated by intracranial tuberculomas.

The main adverse effect of thalidomide has been the development of a peripheral sensory neuropathy leading to some loss of fine touch in the fingers, improved by discontinuing thalidomide, as confirmed by electrophysiological studies. Patients treated with thalidomide and low dose corticosteroids do not experienced relapsing inflammation, in contrast to patients treated with prednisolone as the sole immunosuppressant.

Nevertheless, a double-blind randomized controlled trial[31] which enrolled 47 children with stage 2 or 3 TBM, using thalidomide (24 mg/kg/day orally), as adjunctive therapy to anti-TB drugs and steroids, vs placebo, has been published in 2004. The study was terminated early because all adverse events (worse motor function at 1 month and two deaths) occurred in the thalidomide treatment arm. These results do not support the use of adjunctive high-dose thalidomide therapy in the treatment of TBM.

However, once again, the same Authors assessed the use of thalidomide in not-responding TBM and published them in two further following case reports, in 2006 and 2009 respectively.

The first one[32] described three children with a giant TB abscess, and the fourth with chronic basal arachnoiditis with progressive loss of vision. Three of the four patients had relentless

neurologic deterioration, and all showed disease progression on neuroimaging despite full medical and appropriate surgical treatment. Marked clinical and neuroradiologic improvement occurred after thalidomide was added to the anti-TB treatment regimen of these four patients. So, the Authors suggested that adjunctive thalidomide might have some role in the management of intractable intracranial TB, but it needs further investigation because of adverse effects previously reported.

The second one[33] described a 7-year-old child, on maintenance chemotherapy for acute lymphoblastic leukemia, developed TBM complicated by progressive basal meningeal inflammation and abscess formation, in spite of adequate TB treatment and adjunctive corticosteroid therapy. The child became blind as a result of involvement of the optic chiasm. After 2 months of adjunctive thalidomide therapy, the child regained vision and cranial MRI showed marked reduction of the inflammatory changes previously demonstrated. The present case suggests a role for thalidomide also in the treatment of blindness due to involvement of the optic chiasm in progressive basal TBM.

With regard to TB-HIV co-infection, it's important to refer a study published in 2000, regarding the use of thalidomide in TB-HIV co-infection. In this placebo-controlled study, thalidomide therapy resulted in immune stimulation, increased CD4+ and CD8+ T cell counts, without an increase in plasma HIV levels. In the presence of thalidomide, antigen-specific immune responses *in vitro* and in patients with HIV/TB were enhanced[34].

Reports on similar cases also suggest that interferon-gamma and infliximab (TNF-α antibody) may be helpful, but their use cannot be suggested[35].

Discussion

According to data recently (2008) published on the Cochrane database systematic review[20], corticosteroids improves outcome and death risk in HIV negative children with TBM, but there are no enough evidences to achieve similar conclusions for their use in HIV positive children.

Adverse effects were poorly reported, but those recorded in the trials were infrequent and often mild and treatable. There is no direct evidence to guide selection of the specific corticosteroid to be used in TBM; most trials used dexamethasone or prednisolone, and physicians should use one of these two drugs in clinical practice or for future studies.

There are no data from controlled trials comparing different corticosteroid regimens.

The drug and dose as used in most trials may be dexamethasone (for children 0.3 to 0.4 mg/kg/day for one to two weeks and tapered over the next two weeks) or prednisolone (for children 2 mg/kg/day for three weeks and tapered over the next three weeks)[20].

Nevertheless, the British Infection Society guidelines[36] suggest that all children should be given prednisolone 4 mg/kg/24 h (or equivalent dose dexamethasone: 0.6 mg/kg/24 h) for 4 weeks, followed by a reducing course over 4 weeks, regardless of disease severity at presentation.

Data regarding their use in HIV positive patients are inconclusive. However, there is not enough evidence to support or refute their use in these circumstances.

New randomized controlled trials are needed and they should address whether there is a difference in effectiveness of various corticosteroids; the optimum duration of corticosteroid therapy; whether they reduce mortality and morbidity in HIV positive people with TBM[20].

The clinical application of thalidomide as part of standard TB therapy is not conclusive, because of the variability among reports. In fact, thalidomide has been shown to be an effective adjuvant for TB patients complicated with severe inflammatory reaction or wasting conditions. Although there are good reasons to believe that thalidomide might affected the clinical and radiological course of selected patients positively, a well-done study is needed to clarify the value of thalidomide in TB mass lesions of the CNS. In the light of reported data, it's difficult to establish whether thalidomide may or not affect death rates in patients with late stage CNS-TB. Similarly, it's difficult to explain so different results obtained by the only randomized controlled trial published, in contrast to good results obtained by the other studies (case reports, clinical trials, placebo-controlled studies) reported.

Consequently, thalidomide should not be used for the routine treatment of TBM[36], but it may be helpful as a "salvage therapy" in patients with tuberculomas not-responding or poor-responding to anti-TB drugs and high dose corticosteroids.

References

1) Humphries MJ, Teoh R, Lau J, Gabriel M. Factors of prognostic significance in Chinese children with tuberculous meningitis. Tubercle 1990; 71: 161-168.

2) van Well GT, Paes BF, Terwee CB, Springer P, Roord JJ, Donald PR, van Furth AM, Schoeman JF. Twenty years of pediatric tuberculous meningitis: a retrospective cohort study in the western cape of South Africa. Pediatrics 2009; 123: e1-8.

3) Parsons M. Tuberculous meningitis: A handbook for clinicians. A handbook for clinicians. Oxford: Oxford University Press, 1988: pp. 32-62.

4) Ellard GA, Humphries MJ, Allen BW. Cerebrospinal fluid drug concentrations and the treatment of tuberculous meningitis. Am Rev Respir Dis 1993;148: 650-655.

5) Thwaites GE, Lan NT, Dung NH, Quy HT, Oanh DT, Thoa NT, Hien NQ, Thuc NT, Hai NN, Bang ND, Lan NN, Duc NH, Tuan VN, Hiep CH, Chau TT, Mai PP, Dung NT, Stepniewska K, White NJ, Hien TT, Farrar JJ. Effect of antituberculosis drug resistance on response to treatment and outcome in adults with tuberculous meningitis. J Infect Dis 2005; 192: 79-88.

6) Alffenaar JW, van Altena R, Bökkerink HJ, Luijckx GJ, van Soolingen D, Aarnoutse RE, van der Werf TS. Plasma and CSF pharmacokinetics of moxifloxacin in a patient with tuberculous meningitis. Clin Infect Dis 2009; 49: 1080-1082.

7) van Loenhout-Rooyackers JH, Keyser A, Laheij RJ, Verbeek AL, van der Meer JW. Tuberculous meningitis: is a 6-month treatment regimen sufficient? Int J Tuberc Lung Dis 2001; 5: 1028-1035.

8) The National Collaborating Centre for Chronic Conditions. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London: Royal College of Physicians; 2006.

9) Tahaoğlu K, Ataç G, Sevim T, Tärün T, Yazicioğlu O, Horzum G, Gemci I, Ongel A, Kapakli N, Aksoy E. The management of anti-tuberculosis drug-induced hepatotoxicity. Int J Tuberc Lung Dis 2001; 5: 65-69.

10) Thompson NP, Caplin ME, Hamilton MI, Gillespie SH, Clarke SW, Burroughs AK, McIntyre N. Anti-tuberculosis medication and the liver: dangers and recommendations in management. Eur Respir J 1995; 8: 1384-1388.

11) Green JA, Tran CT, Farrar JJ, Nguyen MT, Nguyen PH, Dinh SX, Ho ND, Ly CV, Tran HT, Friedland JS, Thwaites GE. Dexamethasone, cerebrospinal fluid matrix metalloproteinase concentrations and clinical outcomes in tuberculous meningitis. PLoS ONE 2009; 4: e7277.

12) Coyle PK. Glucocorticoids in Central Nervous System bacterial infection. Arch Neurol 1999; 56:796-801.

13) Brooks WD, Fletcher AP, Wilson RR. Spinal cord complications of tuberculous meningitis; a clinical and pathological study. Q J Med 1954; 23: 275-290.

14) Girgis NI, Farid Z, Kilpatrick ME, Sultan Y, Mikhail IA. Dexamethasone adjunctive treatment for tuberculous meningitis. Pediatr Infect Dis J 1991; 10: 179-183.

15) Girgis NI, Sultan Y, Farid Z, Mansour MM, Erian MW, Hanna LS, Mateczun AJ. Tuberculosis meningitis, Abbassia Fever Hospital-Naval Medical Research Unit No. 3-Cairo, Egypt, from 1976 to 1996. Am J Trop Med Hyg 1998; 58: 28-34.

16) Kumarvelu S, Prasad K, Khosla A, Behari M, Ahuja GK. Randomized controlled trial of dexamethasone in tuberculous meningitis. Tuber Lung Dis 1994; 75: 203-207.

17) Schoeman JF, Van Zyl LE, Laubscher JA, Donald PR. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. Pediatrics 1997; 99: 226-231.

18) Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TT, Nguyen TC, Nguyen QH, Nguyen TT, Nguyen NH, Nguyen TN, Nguyen NL, Nguyen HD, Vu NT, Cao HH,Tran TH, Pham PM, Nguyen TD, Stepniewska K, White NJ, Tran TH, Farrar JJ. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med 2004; 351: 1741-1751.

19) Prasad K, Volmink J, Menon GR. Steroids for treating tuberculous meningitis. Cochrane Database Syst Rev 2000; (3): CD002244.

20) Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev 2008; (1): CD002244.

21) Evans DJ. The use of adjunctive corticosteroids in the treatment of pericardial, pleural and meningeal tuberculosis: do they improve outcome? Respir Med 2008; 102:793-800.

22) Fu LM, Fu-Liu CS. Thalidomide and tuberculosis. Int J Tuberc Lung Dis 2002; 6: 569-572.

23) Sampaio EP, Kaplan G, Miranda A, Nery JA, Miguel CP, Viana SM, Sarno EN. The influence of thalidomide on the clinical and immunological manifestation of erythema nodosum leprosum. J Infect Dis 1993; 168: 408-414.

24) Moreira AL, Tsenova-Berkova L, Wang J, Laochumroonvorapong P, Freeman S, Freedman VH, Kaplan G. Effect of cytokine modulation by thalidomide on the granulomatous response in murine tuberculosis. Tuber Lung Dis 1997; 78: 47-55.

25) Tsenova L, Sokol K, Freedman VH, Kaplan G. A combination of thalidomide plus antibiotics protects rabbits from mycobacterial meningitis-associated death. J Infect Dis 1998; 177: 1563-1572.

26) Tsenova L, Bergtold A, Freedman VH, Young RA, Kaplan G. Tumor necrosis factor a is a determi-

nant of pathogenesis and disease progression in mycobacterial infection in the central nervous system. Proc Natl Acad Sci 1999; 96: 5657-5662.

27) Tsenova L, Mangaliso B, Muller G, Chen Y, Freedman VH, Stirling D, Kaplan G. Use of IMiD3, a thalidomide analog, as an adjunct to therapy for experimental tuberculous meningitis. Antimicrob Agents Chemother 2002; 46: 1887-1895.

28) Schoeman JF, Springer P, Ravenscroft A, Donald PR, Bekker LG, van Rensburg AJ, Hanekom WA, Haslett PA, Kaplan G. Adjunctive thalidomide therapy of childhood tuberculous meningitis: possible anti-inflammatory role. Child Neurol 2000; 15: 497-503.

29) Schoeman JF, Ravenscroft A, Hartzenberg HB. Possible role of adjunctive thalidomide therapy in the resolution of a massive intracranial tuberculous abscess Child's Nerv Syst 2001; 17: 370-372.

30) Robertsa MTM, Mendelsona M, Meyerb P, Carmichaela A, Levera AML. The use of thalidomide in the treatment of intracranial tuberculomas in adults: two case reports. J Infect 2003; 47: 251-255.

31) Schoeman JF, Springer P, van Rensburg AJ, Swanevelder S, Hanekom WA, Haslett PA, Kaplan G. Adjunctive thalidomide therapy for childhood tuberculous meningitis: results of a randomized study. J Child Neurol 2004; 19: 250-257.

32) Schoeman JF, Fieggen G, Seller N, Mendelson M, Hartzenberg B. Intractable intracranial tuberculous infection responsive to thalidomide: report of four cases. J Child Neurol 2006; 21: 301-308.

33) Stefan DC, Andronikou S, Freeman N, Schoeman J. Recovery of vision after adjuvant thalidomide in a child with tuberculous meningitis and acute lymphoblastic leukemia. J Child Neurol 2009; 24: 166-169.

34) Bekker LG, Haslett P, Maartens G, Steyn L, Kaplan G. Thalidomide-induced antigen-specific immune stimulation in patients with human immunodeficiency virus type 1 and tuberculosis. J Infect Dis 2000; 181: 954-965.

35) Coulter JB, Baretto RL, Mallucci CL, Romano MI, Abernethy LJ, Isherwood DM, Kumararatne DS, Lammas DA. Tuberculous meningitis: protracted course and clinical response to interferon-gamma. Lancet Infect Dis 2007; 7: 225-232.

36) Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J; British Infection Society. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. J Infect 2009; 59: 167-187.