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Review article

Osteoarticular Tuberculosis: Clinical complexity, Laboratory challenges, Immunological intrigue

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ABSTRACT

Tuberculosis is a chronic disease caused by *Mycobacterium tuberculosis* and it continues to be a major health problem in developing countries. This problem is further compounded by the emergence of HIV co-infection and multidrug resistant tuberculosis. The majority of diagnosis is made on clinical, radiological grounds along with sputum microscopy. Cytokines reflect the inflammatory microenvironment; hence their study could be helpful in quantifying the progress of the disease and the beneficial effect of the treatment. These could serve as biomarkers signifying the end point of complete clinical and bacteriological cure. In this study we have studied a repertoire of different cytokines in osteoarticular tuberculosis, a paucibacillary disease. Changes in these immune parameters correlated with a significant clinical improvement, thereby providing a better understanding of the immunopathogenesis of the disease.

KEYWORDS: Tuberculosis, osteoarticular, cytokines

INTRODUCTION

Tuberculosis - A Major Public Health Problem

Tuberculosis (TB) is a major public health problem in developing countries. In 2011, 8.7 million people were diagnosed with TB worldwide including 1.1 million cases among people with HIV. About 3.7 percent of new TB patients in the world have multidrug-resistant TB (MDR-TB) and its prevalence is much higher in previously treated patients (approx. 20%). About 60 percent of these cases occur in Brazil, China, India, the Russian Federation and South Africa. Approximately nine percent of MDR-TB cases are extensively drug-resistant TB (XDR-TB). Indian is the highest TB burden country with 2.2 million cases of TB in 2011[1].

Tuberculosis - Chronicity and Latency

Tuberculosis is a chronic disease. As the actively growing bacilli express different antigens due to differences in metabolism, protein secretion and cell wall composition, the immune system is differentially stimulated[2]. Therefore, immune response varies during the course of the disease making it difficult to predict the immunoregulatory response in the disease[3]. Recent research has found that mycobacteria can trigger the production interferon-beta, which is active against viruses. Further it can also block the action of interferon-gamma which helps in the elimination of bacteria[4].

In case of phenotypic drug resistance, prolonged chemotherapy is required due to the presence of non-replicating mycobacteria in the granuloma. Mycobacteria store triacylglycerols under stress. There is a shift from aerobic respiration to anaerobic in dormant bacilli and the genes involved in the beta-oxidation of fatty acids are up-regulated, which in turn serve as a source of energy. Also such sputum samples contain predominantly resuscitation promoting factor (RPF) dependent bacteria which are not detected by culture methods. Such bacteria are found to be

tolerant to rifampicin and require prolonged antibiotic therapy for clearance[5].

Latency is maintained by a fine balance between pathogen persistence and immune response. Staining for acid fast bacilli may not be the detection method of choice as non-replicating mycobacteria exhibit reduced acid fastness due to cell wall remodeling. Isoniazid reduces the risk of disease reactivation in latent TB infection[6].

Mycobacteria have been found to cause the host tissue cells differentiation into virtually any other type of cell, thereby enabling its spread to other parts of the body[5]. Also *M.tuberculosis* is able to infiltrate stem cells in the bone marrow, thereby leading to drug resistance. Studies have found genetic material of the bacteria inside the stem cells, and active bacteria have been isolated from patients who had undergone extensive treatment[7].

Osteoarticular TB

Approximately ten percent of extrapulmonary TB involves bones and joints. Therefore osteoarticular TB accounts for one to three percent of all active clinical TB cases, indicating the burden of disease in the community[8]. The sites affected in decreasing order of frequency are spine, hip and knee[9]. Skeletal TB is characterized by insidious onset, monoarticular or monooseous involvement with constitutional symptoms such as low grade fever, lassitude, anorexia, weight loss and night cries. Local examination reveals painful limitation of movements, muscle wasting and regional lymphadenopathy. In developing countries, where tuberculosis is prevalent, the diagnosis of osteoarticular TB can be reliably made on clinical and radiological examination but not so in affluent societies where TB is a rare disease[10].

Conventional Diagnostic Techniques

The earliest visible radiological sign is localized osteopenia followed by the decrease in joint space and haziness of the articular margins and bony cortices. Later the X-rays show collapse of bone, subluxation, dislocation or deformity of the joint. Changes in the X-rays are appreciated two to four months after the onset of disease. Sequestrum formation and dystrophic calcification are characteristic features of TB[10]. Scintigraphy is extremely sensitive in detecting signs of early skeletal tuberculosis but it may show increased uptake in osteoporotic fractures, infections, stress fractures, healing traumatic fractures, inflammation due to degenerative osteoarthrosis or malignancies. CT Scans can show early lytic lesions, marginal erosions and soft tissue swelling due to tissue edema, granulation, exudation or abscess formation. It is the method of choice for detecting disease in difficult areas i.e. cervicodorsal areas, sacroiliac joint, sacrum, ribs, posterior end of vertebrae and the encroachment of vertebral canal and dystrophic calcification can also be detected. MRI scans show encroachment of vertebral canal, displacement of dural sheath, localized tuberculoma, generalized granuloma, shrinkage of cord substance, myelitis, myelomalacia, syrinx of cord can be seen in T1 and T2 weighted images[10].

Sputum smear microscopy requires 10^4 to 10^5 organisms/ml. The sensitivity of smears in extra-pulmonary samples vary between ten to thirty percent. Sensitivity of smear microscopy can be enhanced by utilizing fluorochrome dyes such as auramine and rhodamine. However, pathogenic and saprophytic mycobacteria cannot reliably be distinguished by smears alone[11]. Cultures on Lowenstein Jensen medium, are positive in 30-60 percent cases. Various methods for detecting early growth of*M.tuberculosis*have been developed which include BACTEC system, MGIT (Mycobacteria growth indicator tube), MB/BacT, Septi-Chek.Histopathologic examination reveals typical tubercles. Examination of synovial fluid in early cases is marginally helpful revealing lymphocytosis; glucose levels decrease while proteins are elevated. Blood findings and Mantoux test may be suggestive of the disease but is not specific for *M.tuberculosis[10]*.

Serological tests are based on antibody detection using native and recombinant antigens including 38KDa, 16KDa, 6Kda, LAM, ESAT-6, CFP-10. However, specificity is poor (<80%) in majority of products. Also HIV coinfection diminishes performance of existing assays. World Health Organisation had issued a warning against the use of serological tests for the diagnosis and treatment of active TB on 20th July, 2011[12]. It was also adopted by Govt. of India.

Newer Diagnostic modalities

Mycobacterial specific phages and reporter genes like luciferase have been used for detection of growth and for assessing the drug susceptibility to anti-TB drugs. Results can be obtained in 48 hours. Rapid identification of mycobacterial isolates includes lipid profiling by HPLC or HP-TLC, hybridization with specific gene probes, polymerase chain reaction-restriction fragment length polymorphism and gene sequencing. When used along with newer methods of detection of the early growth (such as BACTEC, Septi-Chek, MGIT), the isolate can be identified within one to two days. rRNA targeting probes are 10-100 fold more sensitive than DNA targeting; the lowest detection limit is around 100 organisms. Separate gene targets like IS 6110, MPB 64, repetitive sequences, GC repeats, devR, 38kD, TRC 4, IS 1081 have been used. A nested PCR target of IS-1081 has been developed at Centre for DNA Fingerprinting and Diagnostics (CDFD), Hyderabad[11]. The use of IS 6110 had been associated with many false negative results as few *M.tuberculosis* strains in south-east Asia lack or have only one copy of IS 6110. Some false positive results may also occur as some nontubercular mycobacteria also possess IS6110[13].

Cytokines : Biological response modifiers

Cytokines are a group of proteins produced by the cells of the immune system, either as a response to an immune stimulus or as an intercellular signal after certain stimulation. As cytokines reflect the inflammatory milieu, they could serve as biomarkers for potential clinical effect of the therapeutic interventions. ELISA and bead-based multiplex immunoassays are currently the most commonly used techniques to quantify cytokines due to their high specificity and sensitivity. A number of parameters can affect adequate and reliable measurements of cytokine levels in biological specimens including timing of sampling, sample handling and storage, and the choice of samples, plasma or serum[14].

T helper cells

In 1986, Mosmann and Coffman discovered the helper T (Th) cells and classified them as Th1 and Th2, based on

their distinct pattern of cytokine production and function. Till date, various T cell subsets have been characterized including Th1, Th2, Th17 and inducible T regulatory cells (iTreg), which shape the adaptive immune responses and participate in various pathological processes[15]. Th1 cells are a regulator of cellular immunity providing protection against intracellular microorganisms while Th2 cells regulate humoral immunity providing protection against gastro intestinal nematodesand play a role in the pathogenesis of allergic diseases such as asthma[16,17].

During the past decade, a new family of CD4+ T cells characterized by the production of IL-17 was discovered and therefore named TH17 cells[18]. Internal microenvironmental stimuli include a combination of TGF-β, IL-6 and IL-21 which induce the differentiation of naïve T cells into Th17 cells[19]. The development of these cells is inhibited in the presence of Th1 or Th2 cytokines[18,20]. To compound the matters further, the expanding lineage continues to unveil hitherto unknown cell types; two of them are follicular T helper cells (Tfh) and Th9. Tfh cells cause production of IL-21 and are involved in promotion of germinal centre responses and B-cell class switching. Th9 subset is involved in host defence against extracellular parasites, primarily nematodes[21].

Severe abnormalities in the immune response to *Mycobacterium tuberculosis* have been described in people with HIV infection due to the loss of CD4 cells. The risk of reactivation is low in individuals with latent tuberculosis infection and high CD4 T lymphocyte counts[22]. Numerous studies have shown that co-erceted CD4 and CD8 cell function is responsible for effective anti tubercular immunity. Therefore, CD4 cell count or CD4:CD8 ratio can be used to screen patient not responding to antitubercular therapy and immunomodulation may be given to enhance the therapeutic response of drugs[23].

Regulation of bone remodeling

Skeletal homeostasis is dynamically influenced by the immune system. RANKL is the main regulator of osteoclastogenesis. Activated T cells increase the expression of RANKL and thereby promote osteoclasticactivity[24]. Th1 and Th2 cells inhibit osteoclastogenesis by acting on the precursor cells, mainly through IFN-γ and IL-4, respectively. Other cytokines having inhibitory roles on osteoclastogenesis include IL-12, IL-18 and IL-10[25]. IL-17 induces RANKL on mesenchymal cells and promotes osteoclastogenesis, in vitro[26]. Inhibitors of RANKL induced osteoclastogenesis include osteoprotegerin (OPG) which is secreted by the preosteoblasts or the stromal cells[24,27].

A second mechanism by which T lymphocytes may enhance osteoclastogenesis is due to IL-7 production, which appears to be a RANKL independent process. Finally, T cells express tumour necrosis factor (TNF)-α which acts in concert with RANKL to promote osteoclast formation[28]. T cells probably are responsible for bone loss due to a series of pathological conditions as in rheumatoid arthritis or inflammatory bowel disease[29].

When RANKL is absent, GM-CSF enhances progenitor cell proliferation, thereby increasing the number of osteoclasts when these progenitor cells are exposed to RANKL[30]. Together, GM-CSF and RANKL induces expression of genes, including those encoding tartrate resistant acid phosphatase (TRAP), cathepsin K (CATK), calcitonin receptor and β3-integrin leading to the development of mature osteoclasts[27]. Treg cells can suppress osteoclastogenesis and hence, can ameliorate bone resorption and destruction[31].

Cytokine panoply – Search for cues on disease activity and adequacy of treatment?

In our study we tested a repertoire of cytokines and studied the changes in their levels with treatment. This study provided a better understanding of the immunobiology of osteoarticular tuberculosis and hence evaluation of their role as biomarkers for disease progression. With treatment significant rise is seen in the levels of CD4, CD4/CD8 ratio, IL-1, IL-2, IFN-γ, total leucocyte count and lymphocytes while there is fall in levels of IL-10 and TNF-α. Change in these immune parameters signifies clinical improvement; therefore, serial monitoring of various interleukins can help monitor the course of disease.

IFN-γ activates macrophages to effectively eliminate mycobacterium. IFN-γ is the most potent cytokine to induce release of nitric oxide which is toxic to mycobacteria[32]. It also promotes TNF-α production by macrophages and hence better granuloma formation[33]. In our study, following antitubercular therapy IFN-γ levels increased. These findings showed IFN- γ is associated with a Th-1 type immune response and a favorable clinical response[34,35].

IL-1 causes recruitment of phagocytes and along TNF-α it acts as an endogenous pyrogen responsible for fever in TB patients[36,37]. It causes enhancement of IL-6 and TNF-α production, thus helping in maintenance of the granuloma and controlling infection. We have found that IL-1 levels increased significantly with treatment showing that a rise in IL-1 levels is associated with a favourable immune response as shown by previous studies[35,38].

IL-2 is an important T cell growth and differentiation factor and is central to protective immunity against intracellular bacteria. IL-2 induces differentiation of Th0 lymphocytes to Th1 lymphocytes and increases the local concentration of macrophage activating factors, mainly TNF-α[39]. Tuberculosis patients receiving recombinant human IL-2 show clinical improvement and reduced bacterial load[40]. IL-2 drives the immune response to Th-1 type pattern thereby up regulating cellular immunity and helping to control intracellular infections[34]. In our study, there was a significant rise in serum IL-2 level, which was paralleled by improvement in clinical picture, also reported in a previous study[35,41]. The serum IL-2 level was found to be much lower in patients who presented with acute symptoms than with patients with chronic grumbling disease, indicating that patients with chronic symptoms have robust Th1 cell activity[35].

TNF-α is produced by activated macrophages and monocytes in response to mycobacterial antigens causing enhancement of antimicrobial activity[38,42]. The physiological concentration of TNF-α contributes to antimicrobial defense and local production leads to granuloma formation, control of infection and mycobacterial elimination[43]. In our study, there was a fall in the value of this cytokine with treatment which coincided with resolution

of symptoms, a finding that had been observed previously in other studies[33,34,35].

IL-3, a cytokine secreted by activated T lymphocytes, stimulates the proliferation, differentiation and survival of pluripotent hematopoietic stem cells[44]. IL-3 inhibits the development of B cell lineage[45]. IL-3 facilitates the recruitment of neutrophils and eosinophils and regulates their localization to inflammatory sites by acting on the endothelium. IL-3 can also potentiate IgE mediated basophil histamine and LTC4 release probably pointing to an important role in allergic diseases[46] and can promote cell survival by suppressing apoptosis[47]. In our study no correlation was found in the serum levels of IL-3 before and after treatment[48]. Omnibus recruitment of all immune reactive cells and make them available for directional commitment to target the antigenic insult is perhaps not imperative in responses to tubercle bacilli.

IL-12 is produced by dendritic cells, macrophages, neutrophils and microglial cells[49]. IL-12 is a heterodimer formed by a 35 KDa light chain(p35) and 40 KDa heavy chain(p40)[50]. The ability of IFN-γ to enhance production of IL-12 forms a positive feedback during the course of inflammatory Th1 responses. The effects of IL-4 and IL-13 on expression of the gene encoding p40 are bimodal; at early phase of treatment (<24 hours) they inhibit p40 production, whereas later they strongly enhance transcription of the genes encoding both p40 and p35[51]. In our study there was a decrease in the levels of IL-12 with treatment[52]. IL-12, previously known as natural killer cell stimulatory factor or cytotoxic lymphocyte maturation factor, is an early proinflammatory cytokine which is required for initiation and maintenance of cell mediated immunity against intracellular microorganisms[53].

Transforming growth factor (TGF)-β is involved in many cellular processes including cell growth, cell differentiation, apoptosis, cellular homeostasis and other cellular functions. It exists in at least three isoforms - TGF-β1, TGF-β2 and TGF-β3. The TGF-β superfamily includes inhibins, actinin, bone morphogenetic proteins. Langhans giant cells and epitheloid cells in tubercular granulomas express increased levels of TGF-β1 mRNA suggesting its local production may result in deactivation of macrophages leading to immunopathology of the disease[54,55]. To various degrees, TGF-β inhibits T cell proliferation and differentiation and the production of IL-2 and IFN-γ[56,57]. Sustained secretion of TGF-β has also been associated with the induction of a long-lasting state of hyporesponsiveness (anergy) to specific nonselfantigens[58]. In our study, the levels of TGF-β increased post-treatment which is consistent with previous studies[52,59].

IL-10 is a marker of Th2 cell activity and acts as immune inhibitor by downregulation of Th1 responses[60]. It reverses mycobactericidal effect of TNF, suppresses IL-12 production, inhibition of T cell proliferation, and suppression of cytokine production, especially IFN-γ[61]. In our patients the serum IL-10 level was quantitatively higher in non-responders at the start of the study. This indicated inhibition of immunity by IL-10. At three months of follow up, there was significant decrease in serum IL-10 level in the patients who were given immunomodulation along with standard ATT than the patients who were only given standard ATT, indicating improvement in beneficial immune activity. It was seen that patients who had the highest IL-10 levels at presentation, had huge abscesses and resolution of their abscess, together with progressive fall in their IL-10 levels occurred following a combination of standard anti tubercular chemotherapy and immunomodulation[35].

IL-17 family consists of six cytokines, IL-17 A-F. IL-17A and IL-17F share the strongest homology while IL-17E has the least homology with IL-17A[62]. IL-17 stimulates the recruitment of neutrophils and release of microbicidal substances providing defense against various pathogens[63]. Other proinflammatory cytokines such as TNF-α have been shown to have a synergistic effect with IL-17[64]. IL-17 provides barrier integrity against extracellular pathogens by activating immune response in tissues and allowing immunological memory by inducing the recruitment of adaptive immune cells.IL-17 also induces regeneration of epithelial surfaces after inflammation. Th17 cells participate in early inflammatory response to mycobacterial infection and has been shown to be associated with reactivation of latent TB infection[65]. In our study IL-17 was detectable in only one patient, before starting treatment. After treatment however, the value came down to undetectable levels i.e. less than 3.3pg/ml[48]. In our study we had quantified only IL-17A since studies done previously had shown its role in tuberculosis[66]. Since the quantification of other five members of IL-17 family of cytokines has not been done in our study, it is difficult to comment on the exact nature of Th17 response in osteoarticular tuberculosis in our patients.

In summary, constant expression of cellular immunity is required to control growth of *M.tuberculosis* but an intricate consequence of this event is that it can also result in chronic inflammation and pathologic end result. During primary tuberculosis both IFN-γ and IL-17 producing cells are induced, both are potent inflammatory cytokines capable of inducing expression of chemokines that promote cell recruitment and granuloma organization throughout infection. During the chronic phase, a balance between Th1 and Th17 responses needs to be achieved to control bacterial growth and limit immunopathology. Thus, the regulation of Th1 and Th17 responses during tuberculosis is essential to promote anti-mycobacterial immunity and to prevent extensive immunopathologicalconsequences[18]. IL-17 is implicated in inflammatory diseases such as psoriasis, asthma and inflammatory bowel disease and causes the development of lesions associated with multiple sclerosis and rheumatoid arthritis[19,62].

Qualitatively, the various cytokine molecules do not exhibit much difference in responders and non-responders. However, in the responders, the quantitative levels of functionally disparate cytokines exhibit an emphatic difference. Extension of this line of exploration to a larger series of subjects may yield a tangible outcome to indicate the adequacy of intervention (Table 1,2).

Table 1 : Categorization of patients

Groups	Number of Patients
*Responders	132
†Non-responders	23
Total	155

*Responders : Patients who responded to antitubercular treatment given for 12-15 months
†Non-Responders : Patients in whom treatment was extended or showed deterioration of disease/appearance of additional lesions despite multidrug treatment or recurrence of previously healed lesions or non-healing wound following surgery

Table 2 : Cytokine profile of patients

Groups		Cytokines	Before treatment (mean)*	After treatment (mean)*	p value
Responders	Signaling molecule	IL-1	4.53	21.54	0.000(S)
		IL-3	393.26	294.26	0.760(NS)
		TNF-α	50.85	36.85	0.000(S)
	Th1	IL-2	8.53	34.08	0.000(S)
		IFN-γ	9.54	44.92	0.000(S)
		IL-12	249.88	154.05	0.000(S)
	Th2	IL-10	30.31	6.77	0.000(S)
	Suppressive/ Regulatory	TGF-β	172.75	425.86	0.000(S)
		IL-17	0.5711	0.00	0.269(NS)
Non-Responders	Signaling molecule	IL-1	6.00	15.50	0.001(S)
		TNF-α	56.00	51.00	0.040(S)
	Th1	IL-2	4.00	31.75	0.000(S)
		IFN-γ	8.75	29.75	0.000(S)
	Th2	IL-10	30.75	21.50	0.136(NS)

*pg/ml

Cytokine Gene Polymorphism

The immune responses in various human diseases differs significantly among individuals. These include changes in the expression and production of cytokines or their receptors. In vitro gene expression studies attempt to determine a genetic basis for such differences. This is achieved by examining the relationship between individual polymorphic alleles or haplotypes of cytokine genes and the expression of the transcript or cytokine in vitro. The main approaches used include measuring the levels of cytokine or cytokine receptor mRNA, or of cytokine or receptor protein, expressed as a result of in vitro stimulation of cells in culture with a mitogen; and isolation of individual alleles by cloning them adjacent to a reporter gene in an expression vector, followed by transfection of an appropriate cell line and measurement of reporter protein expression.

In vivo disease association studies attempt to identify immunogenetic markers for a given disease. Association is sought between specific cytokine gene polymorphisms and clinical outcome by direct comparison of individual cytokine genotypes and the clinical features of the disease[67]. Cytokine gene polymorphisms including TNF-α, IL-1β, IL-6, IL-8, IL-10 and IL-18 had been implicated in the pathogenesis of active tuberculosis[68].

Immunomodulation

The concept of immunotherapy was introduced by Koch in 1890-91 when he used repeated injections of old Tuberculin. Sphalinger reported remarkable successes with modification of Koch's therapy in 1930's only a decade before the advent of chemotherapy. Thus the modern approach is not simply to boost immunity but to replace an inappropriate response by an appropriate one[69].

Many workers have suggested immunotherapy with *Mycobacterium vaccae*which has been found to prevent further tissue destruction and restore protective immunity against the causative organism by causing a Th2 to Th1 shift[70]. BCG has been observed to stimulate the reticuloendothelial system and induces Mycobacterium-specific antibody responses with an isotype profile characteristic of Type I cytokine bias[10,71].

Levamisole has been shown to improve T cell mediated immunityand has been used in Hodgkin's disease, rheumatoid arthritis, and in adjuvant chemotherapy of colorectal cancer[72,73]. Triple antigen (DPT) also provides a generalized broad based immunostimulatoryeffect[74].

Overall in our study it was observed that immunomodulation with BCG, levamisole and DPT vaccine induced a Th-1 type immune response that helped in controlling the progressive tissue destruction associated with tubercular infections. This was also associated with a rise in

IL-1, IL-2 and IFN-γ and a significant fall in ESR, IL-10 and TNF-α[35] (Table 3).

Table 3 : Effect of Immunomodulation on cytokine levels

	Cytokines	Before Immunomodulation* (mean)	After Immunomodulation* (mean)	P value
Signaling molecules	IL-1	15.50	30.75	0.000(S)
	TNF-α	51.00	2.75	0.000(S)
Th1	IL-2	31.75	48.25	0.000(S)
	IFN-γ	29.75	62.25	0.002(S)
Th2	IL-10	21.50	4.50	0.000(S)

*pg/ml

Treatment and Drug Resistance

The treatment of osteoarticular TB includes general measures such as rest and proper immobilization in active disease followed by gradual mobilization as the healing progresses. Multidrug regime of antitubercular drugs, consisting of all first line drugs, is usually employed in active disease. Streptomycin is used paraoperatively. Currently tuberculosis is treated with an initial intensive 2-months regime comprising of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol[75]. The therapy is then continued in maintenance phase to kill the persisters or dormant bacilli. Some prefer to give antitubercular drugs for a minimum of one year, preferably upto eighteen months[10].

Non responsiveness to standard treatment is usually due to acquired or genetic resistance of the infective organism to the drugs being administered or due to any peculiarity of the lesion such as gross destruction of bone or presence of large sequestra. Atypical mycobacterial infections, abuse of broad spectrum antibiotics, poor compliance of patients have led to development of MDR-TB. Of recent occurrence is Super-extensive drug resistance (XXDR) which is defined as resistance to all drugs that are being tested by conventional drug susceptibility testing, including all the second line drugs. Various salvage regimens been proposed such as that by Carl Mendel of the Global TB alliance, hypothetically combining TMC207, OPC67683, PA824 and PNU100480 as a new regimen. At the Hinduja hospital in Mumbai, salvage regimens including combinations of drugs like linezolid, clofazamine, meropenem-clavulanate and thioridazine, are being tried in such patients[76].

Conclusion

Duration of therapy and its cessation continue to remain an unresolved conundrum in osteoarticular tuberculosis. Healthcare provider is helplessly under the guidance of clinical-experience dictated empiricisms rather than science-predicated objectivity. Circulating cytokines is an option to reveal the state of clinical disease but the complex mix of multiple cytokines, exhibiting pleiotropic effects, interacting with each other in a microenvironment under an intriguing web of interconnected regulatory control does not readily offer any easy option for arriving at a classical interference with certainty. Nonetheless, there is an element of consistency in the cytokine levels in parallel with disease activity, recognized by the host immune system as an antigenic insult. This characteristic feature of the cytokine may be exploited to provide a clue about the adequacy of therapeutic intervention. Further fine-tuning is possible by an analysis of the transcriptome of the cytokines rather than soluble cytokines in circulation. In-depth exploration may require the co-mingling of clinical, laboratory and basic sciences.

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