^{99}Tc-MDP treatment for the therapy of rheumatoid arthritis, choroidal neovascularisation and Graves' ophthalmopathy (Review)

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Abstract. Technetium 99 conjugated with methylene diphosphonate, which is an anti-inflammatory drug, can inhibit macrophage infiltration and downregulate a number of proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-1β. Recently, numerous studies have indicated that it could improve rheumatoid arthritis (RA) activity by upregulating the frequency of peripheral γδ T cells and cluster of differentiation $CD4^+CD25^+Foxp3^+$ Tregs, affecting the serum cytokine environment, inhibiting osteoclast formation and reducing the concentrations of rheumatoid factor-immunoglobulin M (IgM)/IgG/IgA. As well, it may have a therapeutic role for choroidal neovascularisation (CNV) and Graves' ophthalmopathy (GO). Therefore, it will be a valuable choice in the treatment of RA, CNV and GO.

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1. Introduction

Technetium 99 (^{99}Tc) conjugated with methylene diphosphonate (MDP) is an anti-inflammatory drug patented in China (patent no. ZL94113006.1), which has been used for the safe and effective treatment of rheumatoid arthritis (RA) and ankylosing spondylitis in China since 1997 (1). ^{99}Tc-MDP treatment can inhibit macrophage infiltration together with the downregulation of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), in addition to intercellular adhesion molecule-1 (ICAM-1) and matrix metalloproteinases (MMPs) (1).

^{99}Tc-MDP is the radioactive-safe decay product of ^{99}mTc-MDP and has been widely used in bone scintigraphy as a radioactive agent with limited radioactivity (demonstrated as harmless to the human body). The present study reviews the therapeutic use of ^{99}Tc-MDP in clinical diseases and the associated mechanisms of action.

2. Rheumatoid arthritis

RA is a chronic, progressive and inflammatory autoimmune disease (2-4), particularly affecting elderly people (5). Although it can affect numerous tissues and organs, it primarily involves flexible joints (6) resulting in synovitis, pannus formation (7) and massive bone destruction with consequent inflammation, pain and disability (8), associated with higher mortality as compared to the general population (9,10).

^{99}Tc-MDP was treated intravenously to active RA patients at a dose of 20 μg/day consecutively for 10-14 days, and reported that the frequency of peripheral cluster of differentiation 3 ($CD3^+$) $\gamma\delta^+$ T cells and $CD4^+$ $CD25^+$ $Foxp3^+$ Tregs were significantly elevated, paralleled with decreased serum TNF-α and IL-6 levels and increased serum TGF-β. There was a positive correlation between the elevation of peripheral CD3+ γδ+ T cells and increased serum transforming growth factor (TGF)-β and decreased disease activity, indicating that ^{99}Tc-MDP may improve RA activity by upregulating frequency of peripheral γδ T cells and $CD4^+$ $CD25^+$ $Foxp3^+$ Tregs, as well as affecting the serum cytokine environment (11).

Ji *et al* (12) isolated peripheral blood mononuclear cells from RA patients and cultured them in medium with 25 μg/l of receptor activator of nuclear factor-κB ligand (RANKL), 25 μg/l macrophage-colony stimulating factor and various concentrations of ^{99}Tc-MDP (5, 10, 20 and 50 mg/l), and found that after 12 or 16 days of culture, large multinuclear

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cells were observed, and that ^{99}Tc-MDP markedly inhibited the changes. Those inhibitory effects were positively associated with the increased ^{99}Tc-MDP concentration, indicating protective effect of ^{99}Tc-MDP on RA via inhibition of osteoclast formation.

Similarly, Gong *et al* (13) reported that 0.01 μg/ml ^{99}Tc-MDP significantly inhibited RANKL-induced osteoclastogenesis with no cytotoxicity, and significantly abolished the appearance of multinucleated osteoclasts, inhibited the expression of the transcription factors c-Fos, nuclear factor of activated T cells and inflammatory factors, such as IL-6, TNF-α and IL-1β. Thus, ^{99}Tc-MDP has anti-osteoclastogenic activity on RANKL-induced osteoclast formation.

After 0.2 g of ^{99}Tc-MDP was administered daily by intravenous drip for 5 days to RA patients and patients with joint pain/arthritis, the injection A and B models of ^{99}Tc-MDP were used with one set daily for 10 days, which was one course of treatment. The next course started after 10 days. Each case used it for 2-4 courses of treatment. In the RA patients, the concentrations of rheumatoid factor-immunoglobulin M (RF-IgM) were 296.2±108.4, 189.5±92.3 and 107.8±72.5 IU/ml; the concentrations of RF-IgG were 325.6±126.2, 209.7±98.2 and 160.2±80.8 IU/ml; and the concentrations of RF-IgA were 330.4±136.3, 210.7±89.2 and 148.8±72.2 IU/ml prior and subsequent to 2 and 4 courses of treatment, respectively. The concentrations of the aforementioned RFs were significantly lower following 2 and 4 courses compared to those prior to treatment ($P<0.05$ and $P<0.01$, respectively). Consequently, ^{99}Tc-MDP appeared to reduce the abnormally high concentrations of RFs, implicating that ^{99}Tc-MDP could have an important role in controlling the activities of RA (14).

Wu *et al* (15) also demonstrated that ^{99}Tc-MDP could suppress the secretion of IL-1 and soluble IL-2R in RA patients.

3. Choroidal neovascularization

Choroidal neovascularisation (CNV), a common vision-threatening complication (16), accounts for 90% of cases of severe vision loss in patients with advanced age-related macular degeneration (17-19). Its pathogenesis involves a disruption of the homeostasis between the retinal pigment epithelium and Bruch's membrane (20). The proliferating choroidal blood vessels extend into the macula region of the subretinal space, and leak fluid, leading to serous retinal detachment and scarring (20) and central vision loss.

Lai *et al* (1) used C57BL/6J mice to induce CNV by laser photocoagulation, and following this they intraperitoneally injected ^{99}Tc-MDP at the doses of 0.05, 0.1 and 0.2 μg/kg or the same volume of phosphate-buffered saline (PBS) daily. After 7 days, areas of CNV were significantly suppressed by ^{99}Tc-MDP treatment without toxicity to the retina, compared with PBS treatment, in a dose-dependent manner. ^{99}Tc-MDP treatment of 0.05, 0.1 and 0.2 μg/kg suppressed the development of CNV by 36.12, 58.76 and 73.48%, respectively. Furthermore, ^{99}Tc-MDP treatment inhibited the infiltration of macrophages to CNV and the downregulation of protein expressions of vascular endothelial growth factor (VEGF), ICAM-1, TNF-α, and MMPs. At the same time, ^{99}Tc-MDP also inhibited VEGF-induced migration and capillary-like tube formation of endothelial cells. In consequence, anti-inflammatory treatment with ^{99}Tc-MDP has therapeutic potential for CNV-related diseases.

4. Graves' ophthalmopathy

Graves' ophthalmopathy (GO), also known as thyroid-associated ophthalmopathy, is an organ-specific autoimmune disease (21,22).

In the general population, the estimated incidence of GO is 16 women and 3 men per 100,000 population per year (23,24), and it is clinically present in 20-25% of patients at the time of their diagnosis of hyperthyroidism (23,25). The exact etiology and underlying mechanism of GO remain to be elucidated. The natural history of GO varies from spontaneous remission to persistent or progressive disease (23,26), and glucocorticoid therapy is the primary treatment (23,27-29).

Yan *et al* (30) incubated retroocular fibroblasts of GO patients for 72 h with 100 U/ml interferon-γ, 100 U/ml IL-1 or 100 U/ml TNF-α in the presence of 99Tc-MDP, recognizing that at base conditions, the percentage of positive cells of human leucocyte antigen-DR (HLA-DR) and ICAM-1 on retroocular fibroblasts was 6.70±3.06 and 5.29±3.02%, respectively, and the synthesis of hyaluronic acid (HA) was 337.8±42.7 ng/ml. Compared to the basal values, 72 h incubation with the aforementioned cytokines clearly enhanced the expression of HLA-DR and ICAM-1 together with the synthesis of HA. In addition, ^{99}Tc-MDP inhibited cytokine-induced retroocular fibroblasts activation and proliferation in a dose-dependent manner.

Pan *et al* (31) evaluated the efficacy of immunosuppressive agents, ^{99}Tc-MDP and the two together in treating patients with GO, finding that in 22 patients treated with immunosuppressive agents, the general efficacy rate was 19/22, and the incidence rate of a serious side effect was 8/22. In 20 patients treated with ^{99}Tc-MDP, the general efficacy rate was 17/20, and the incidence rate of a serious side effect was 2/20. In 24 patients treated with immunosuppressive agents and ^{99}Tc-MDP, the general efficacy rate was 22/24, and the incidence rate of a serious side effect was 2/24. The results suggested that using immunosuppressive agents in combination with ^{99}Tc-MDP could obtain satisfactory efficacy, and avoid the serious side effect and 'rebound' of symptoms in the treatment of GO (31).

5. Conclusion

^{99}Tc-MDP may have numerous important roles in the therapy of clinical disease, as it can improve the activity of RA, treat CNV-related diseases, and avoid the serious side effect in the treatment of GO in combination with immunosuppressive agents, thus, it will be a valuable choice for the treatment of RA, CNV and GO.

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