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ORIGINAL ARTICLE

# Efficacy of rapamycin in patient with juvenile rheumatoid arthritis

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## Summary

Juvenile rheumatoid arthritis (JRA) is an immune-mediated disease characterized by articular inflammation and subsequent tissue damage that may result in severe disability. Several combinations of drugs, including immunosuppressive agents have been used to control disease progression. Although there is no information available on rapamycin efficacy in JRA, it has demonstrated a potential to inhibit inflammatory processes observed in adult rheumatoid arthritis (RA). We present a 21 years old renal transplant recipient with JRA, primarily treated with tacrolimus and steroids, who achieved a long-term disease remission after introduction of rapamycin. As long as pathogenesis of JRA and RA is similar, we conclude that rapamycin could be promising immunosuppressant for patients after renal transplantation suffering from both JRA and RA.

## Introduction

Juvenile rheumatoid arthritis (JRA) is an immune-mediated chronic inflammatory process. Polyarticular exacerbation, treatment inefficacy, concomitant disease or intolerance to therapy represent the reasons that often require hospital admission. As there is no known cure for JRA, treatment is not well standardized and various combinations of nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, glucocorticoids, disease-modifying antirheumatic drugs and immunomodulatory compounds are used. Immunosuppressive agents, such as cyclophosphamide and cyclosporine have been clinically used to control disease progression.

A novel immunosuppressive agent, rapamycin inhibits a serine-threonine kinase, mammalian target of rapamycin (mTOR). Because of the widespread involvement of mTOR in multiple signaling pathways, the inhibitory effect of rapamycin disables virtually all responses to cytokine mediators [1]. Although there is no clinical evidence for its efficacy in arthritis, some experimental data suggest that rapamycin can control synovial fibroblast proliferation in RA by inhibition of platelet derived growth factor (PDGF) [2]. There is evidence that proliferation of synovial fibroblasts and invasive growth in rheumatoid arthritis (RA) is because of impaired regulation of the cell cycle, i.e. the balance between proliferation and physiological cell death (apoptosis). Rapamycin was shown to alter the sensitivity to apoptosis in rheumatoid synovium [3].

## Case report

We present a 21 years old renal transplant recipient. Polyarticular form of JRA was diagnosed at the age of 4 years. Combinations of glucocorticoids, methotrexate, hydroxychloroquine and chlorambucil were used with moderate success. The patient developed secondary amyloidosis, which resulted in renal insufficiency. At the age of 15 years he started peritoneal dialysis. For the following 3 years remission of JRA was observed, during which period patient remained on glucocorticoid monotherapy. In September 2000, at the age of 18 years he received two

**Table 1.** Markers of inflammation, blood morphology, disease activity score, height and body mass before rapamycin administration, after 8 and 18 months of therapy.

| | DAS28 (3)-CRP | HCT (%) | Hb (g/dl) | WBC (G/l) | ESR (1/mm) | CRP (mg) | ALP (U/l) | Body mass (kg) | Height (cm) |
|---|---|---|---|---|---|---|---|---|---|
| Before rapamycin introduction | 5.62 | 35.6 | 11.4 | 12.4 | 25 | 159 | 2555 | 23 | 134 |
| After 8 months of treatment | 2.2 | 42 | 14.1 | 9.6 | 12 | 12.5 | 759 | 25 | 135 |
| After 18 months of treatment | 1.86 | 39.9 | 13.3 | 7.1 | not done | <6 | 630 | 31 | 136 |

DAS, disease activity score; HCT, hematocrite; Hb, hemoglobin; WBC, white blood cells; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ALP, alkaline phosphatase.

kidneys from a 3 years old donor. Post-transplant immunosuppression consisted of glucocorticoids, mycofenolate mofetil (MMF) and FK-506. MMF was soon converted to azathioprine because of diarrhea (future biopsy of jejunum revealed amyloid accumulation). Despite intensive immunosuppression, morning joints stiffness and pain reappeared after transplantation. Twenty joints were painful including proximal interphalangeal joints, wrists, elbows, knees, ankles and hips [disease activity score 28(3)-CRP in Table 1]. NSAIDs, calcitonin, calcium supplementation and calcitriol did not improve patient's condition. Markers of active inflammatory process were positive.

In April 2001 Azathioprine was withdrawn because of hepatotoxicity. In June 2001 the X-ray of the hip joints and iliac bones revealed osteopenia, bone erosions and malformation of the articular heads (Fig. 1).

In the same month rapamycin was administered with simultaneous FK-506 dose reduction. Rapamycin serum trough level was maintained between 4.9 and 8.0 ng/ml. After 6 weeks excellent improvement of patient's general condition was obtained. Inflammation markers decreased gradually (Table 1). Radiological examination in March 2002 revealed progression of osteopenia, increase in number of erosions, flattening of femoral head and subchondrial sclerosis of the joint surface (Fig. 2).

Regression of these changes was observed in January 2003 – X-ray revealed healing surface of the hip joint

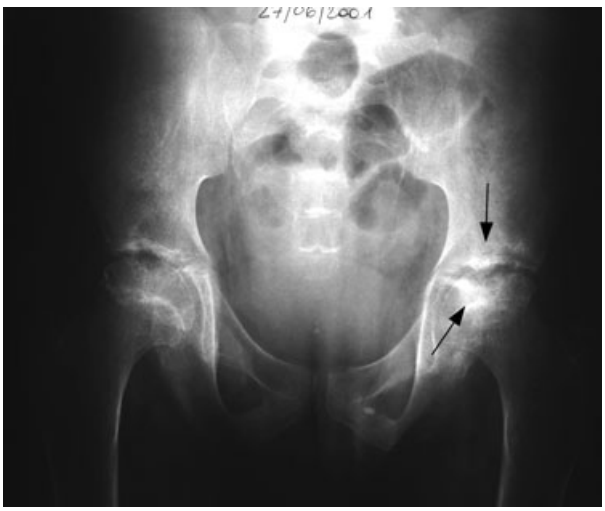

**Figure 1** X-ray of the hip joints before introduction of rapamycin – June 2001.

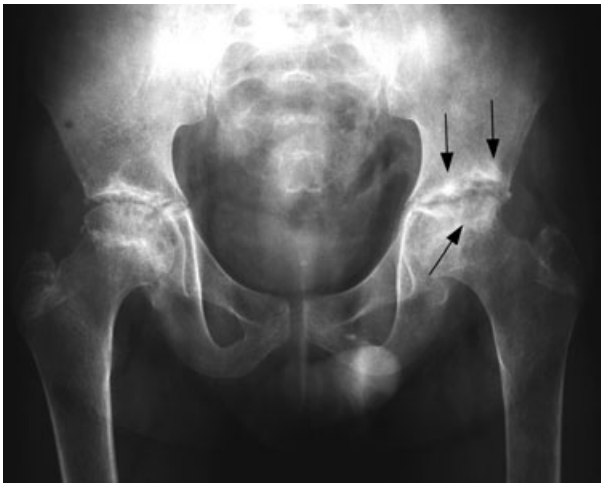

**Figure 2** X-ray of the hip joints in March 2002.

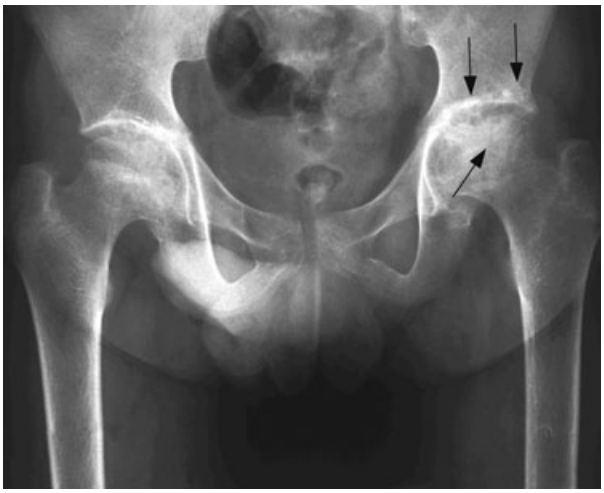

**Figure 3** X-ray of the hip joints in January 2003.

sockets and decreased number of erosions. Destructive changes were present profoundly, whereas cartilage seemed to recover (Fig. 3).

## Discussion

Presented case demonstrates that rapamycin might induce remission of JRA in patients after renal transplantation. The disease is characterized by chronic synovitis, which leads to cartilage and joint destruction. Recent experimental studies bring evidence that rapamycin may influence some factors, which are involved in the pathogenesis of chronic inflammation and cartilage destruction in JRA. Interleukin 10 (IL-10) is an anti-inflammatory cytokine produced in the joint in RA by macrophages and infiltrating blood lymphocytes. Rapamycin *in vitro* has a potential to suppress IL-10 production by RA macrophages dose-dependently [4]. Additionally, rapamycin can inhibit the expression of interleukin 16, which is provoked by IgG in patients with active RA [5]. It has been also demonstrated that rapamycin augments the sensitivity of rheumatoid synovial fibroblasts to apoptosis by down-regulating *bcl-2* gene expression [3]. These observations could explain potential beneficial effects of rapamycin in our patient.

Some readers may be sceptical about the association of rapamycin administration and remission, because this patient already had a 3-year remission on glucocorticoids alone. But, we think that remission between 15 and 18 years of age could have been associated with dialysis itself. Moreover, remission at 6 weeks after rapamycin introduction is when one may anticipate such an effect to occur. No other drugs that could modify JRA have been introduced at the same time.

We conclude that rapamycin could be promising immunosuppressant for kidney transplant recipients suffering from JRA. As long as pathogenesis of JRA and RA is similar, we think that rapamycin could be promising immunosuppressant for both groups of patients.

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