Longitudinal study of Clinical and Quantitative MR Characterization of the Knee in Children with Juvenile Rheumatoid Arthritis

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Introduction

Quantitative evaluation of dynamic contrast enhanced MR imaging (DCE-MRI) in the knees of children with a history of juvenile rheumatoid arthritis (JRA) has been suggested to help monitor the degree of inflammation and therapeutic response during the early phase of the disease (1, 2). In this regard investigating the utility of DCE-MRI as a quantitative method to evaluate disease activity is very important. Specifically, the changes in the values of pharmacokinetic (PK) parameters from longitudinal studies have to be investigated. For this purpose longitudinal study on 17 subjects with JRA was performed at three time points: enrollment, 3 months, and 12 months. The longitudinal study included quantitative DCE-MRI based on pharmacokinetic (PK) modeling, clinical and laboratory assessment. The pharmacokinetic model employed gives three parameters, $K^{trans'}$ (min^{-1}) , k_{ep} (min^{-1}), and $V_{p'}$

Materials and Methods

Knees of 13 children (10 female and 3 male, age: 6 to 16 years, mean 10.2), with a history of JRA were imaged at three different time points: enrollment, 3 months and 12 months. Children were treated with one or several of the following medications (Methotrexate, Relafen, Naroxen, and Ibuprofen) after their first imaging session. T1-weigthed perfusion imaging, with a 3D-GRE sequence, during and after intravenous (i.v) bolus of Gd-DTPA was performed with the following parameters: TR/TE=4.8/1.6, flip angle = 60^0, 128 x 128, 0.5 NEX, 0.8 phase FOV, and 12 sections per 3D slab on 1.5 T GE LX scanner using a quadrature transmit/receive extremity coil. A single bolus dose of 0.1 mm/kg Magnevist® was administered by i.v. injection. Post contrast sequential perfusion T1-weighted images were obtained every 5 sec for 40 data sets (200 sec total acquisition time).

For an open two compartmental pharmacokinetic (PK) model, with isodirectional permeability, the signal intensity in the tissue is given by (1, 2, 3):

$$\frac{S_t(t)}{S_0} - 1 \approx K^{trans'} \sum_{i=1}^{3} \frac{A_i}{k_{ep} - \lambda_i} \left[e^{-\lambda_i (t - tlag)} - e^{-k_{ep}(t - tlag)} \right] + V_p' \sum_{i=1}^{3} A_i e^{-\lambda_i (t - tlag)} \qquad [1]$$

where S_0 and $S_t(t)$ = MRI signal over the tissue, respectively, before and after contrast, $K^{trans'} = (T_{10t} \cdot r_{1t} \cdot \alpha) K^{trans}$, $V_p' = (T_{10t} \cdot r_{1t} \cdot \alpha) v_p$ (where T_{10t} = value of T_1 before contrast over the tissue and r_{1t}= relaxivity in tissue, K^{trans} = transfer constant and is related to the permeability (P), surface area (S) and tissue density (ρ), $K^{trans} = PS\rho$), $k_{ep} = K^{trans}/v_e$ (where v_e is the fraction of interstitial/leakage space), v_p = fraction of plasma space, *tlag* = the arrival time of the contrast in the ROI, and α (mM) is a proportionality factor between the popliteal artery signal enhancement and plasma concentration (α were set to 1) (2). Data analysis was performed with Microsoft® Excel and IDL (RSI, Inc., Boulder, CO)

The clinical measures included physician global assessment (PGA), total active joint (TAJ), total knee score (TKS), and childhood health assessment questionnaire disability index (CHAQ-DI). The laboratory measures included erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

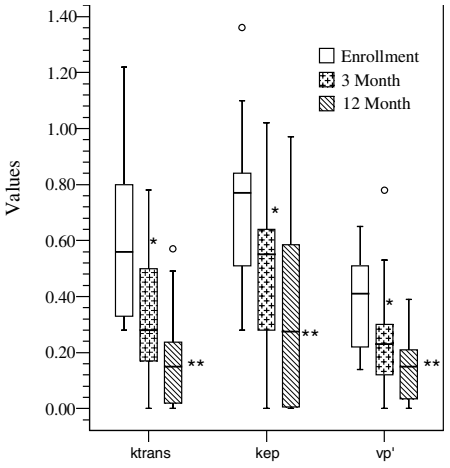

Figure 1. Comparison of the 3 month and 12 month values to enrollment. PK parameters showed significant reduction. At 3 months, *: p = 0.003, p = 0.047, and p = 0.02 (for $K^{trans'}$, k_{ep}, and V_p' respectively) and at 12 months, **: p = 0.001, p = 0.005, and p = 0.002 (for $K^{trans'}$, k_{ep}, and V_p). The Comparisons were based on Wilcoxon signed rank test.

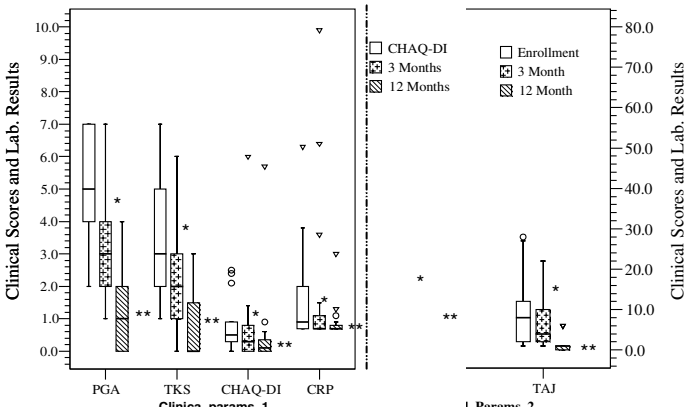

Figure 2. Comparison of the 3 and 12 months values to enrollment. Most clinical parameters indicated significant reductions: at 3 months, *: p = 0.02, p = 0.03, p =0.13, and p = 0.01 (for physician global assessment (PGA), total Active joints (TAJ), childhood health a assessment questionnaire disability index (CHAQ-DI), and total knee score (TKS), respectively) and at 12 months, **: p < 0.001, p = 0.001, p = 0.02, and p = 0.002 (for PGA, TAJ, CHAQ-DI, and TKS, respectively). The C-reactive protein (CRP) also showed a significant decrease at both 3 and 12 months (*: p = 0.007 and **: p = 0.005, respectively); and the erythrocyte sedimentation rate (ESR) at 12 months decreased significantly (**: p = 0.003) but not at 3 months (*: p = 0.35). The Comparisons were based on Wilcoxon signed rank test.

Results and Discussion

The final pharmacokinetic parameters obtained from the fitting the synovial enhancement data by Eq. [1] were $K^{trans'}$, k_{ep}, and V_p'. When compared to the enrollment values all PK parameters, clinical and laboratory measures at 3 months and 12 months showed a significant decrease ($p < 0.05$), except for the CHAQ-DI (p = 0.13) and CRP (p = 0.35) at 3 months. The PK average values at each time point were also compared to the clinical and laboratory assessment and showed excellent correlation in most comparisons.

Conclusions

The absence of meaningful synovial enhancement might be considered as an indication of the healing processes. The decrease of PK, clinical, and laboratory parameters might reflect diminution of disease activity. Hence, PK parameters could be used as an objective follow-up of JRA patients. More longitudinal studies and comparison with clinical outcome measures are required to strengthen these findings.

Reference

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