Vascular Permeability Change As an Imaging Biomarker for Disease Progression and Efficacy of therapeutic intervention of Rheumatoid Arthritis: DCE-MRI Study

Jang Woo Park[1], Hui-jin Song[1], Hee-Kyung Kim[1], Jeehye Seo[1], Seong-Uk Jin[1], Jong Su Baeck[1], Moon Han[1], Yongmin Chang*[2,3], and Young-Hwan Lee*[4]

[1]Medical & Biological Engineering, Kyungpook National University, Daegu, Daegu, Korea, [2]Diagnostic Radiology, School of Medicine, Kyungpook National University, Daegu, Daegu, Korea, [3]Molecular Medicine, School of Medicine, Kyungpook National University, Daegu, Daegu, Korea, [4]Radiology, Daegu Catholic University Medical Center, Daegu, Daegu, Korea

Introduction

There is no single 'gold standard' method to diagnose disease progression in rheumatoid arthritis (RA). Two quantitative indices which are widely used in clinical trials are the American College of Rheumatology Core Data Set and the disease activity score [1]. However, novel imaging biomarker is seldom studied for disease progression in RA. In the present study, we investigated the changes of synovial vascular permeability associated with disease progression using a novel pharmacokinetic model of the distribution of contrast media to dynamic contrast enhanced (DCE) MRI data from animals with RA. Furthermore, we also investigated whether the changes in vascular permeability may signal the efficacy of therapeutic intervention

Material and Methods

RA model which is a murine collagen-induced arthritis (CIA) model was made using the previously described method [3]. To confirm progression level in RA, do vessel stain in ankle of mice. The average body weight of DBA/1J mouse was approximately 25 g. Four groups which are normal mice (N=5), early arthritis mice (N=5), active arthritis mice (N=5) and late arthritis mice (N=5) were used to investigate disease progression from *in vivo* experimental. Two groups which are methotrexate (MTX)-low dose (N=5) and -high dose (N=5) groups were used to investigate the efficacy of therapeutic intervention from *in vivo* experimental. MTX-low dose and -high dose groups were administered each MTX 0.5mg/kg and MTX 1.0mg/kg from booster injection time to active state time.

To obtain DCE MRI, used T1-weighted CA which is Gd-DOTA (DOTAREM, Guerbet France). All magnetic resonance images were obtained using GE Excite 1.5T scanner (GE Healthcare, Milwaukee, WI, USA) with home-made small animal RF coil which is the receive-only, 1-channel, band-pass birdcage type and the inner diameter of the coil was 50 mm. The DCE-MRI parameters for the T1-weighted SE sequence were as follows: echo time (TE) = min, repetition time (TR) = 300 ms, receive bandwidth (BW) = 15.63 kHz, field of view (FOV) = 7 cm, slice thickness = 1 mm, number of excitation (NEX) = 4, spacing = 0, matrix = 192 x 128, phase FOV = 0.5, and scan time = 1min 20sec. MR images were obtained pre- and post- Gd-DOTA (0.1 mmol Gd/kg) by tail vein. Post MR images were dynamically obtained during approximately 2 hours.

The permeability value was calculated using previously published method based by Tofts and Kermode [2]. For positioning the regions of interest (ROI) around knee joint, the contrast enhanced T1-weighted MR images were used as a guide. The size of ROI was kept constant (radius, 3-6mm), and ROI were manually drawn by an experienced expert in radiology, who was blinded to the results. Positioned ROI was used on the permeability map of selected slice for average permeability value of around knee joint. The statistical package for the social sciences 18.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. The result data are expressed as the mean plus or minus SEM. Each group of data set was tested for normality. There are four groups, so one-way analysis of variance (ANOVA) was used. Significance level of statistical tests was set at p-value < 0.05 in the post-hoc analysis.

Results and Discussion

Fig. 1 shows the level of Rheumatoid arthritis by staining CD31 at knee tissue. The mean of the volume normalized transfer rate between plasma and rheumatoid arthritis EES are shown in Table 1. Control group has the lowest permeability value and active group has the highest permeability value. Early group and late group have the similarity permeability value, respectively. The result of one way ANOVA in disease progression was presented in Table 2. Permeability color map was shown this result in Fig 2. Color of control mouse's tissue around knee was the darkest. In contrast, active level mouse was the brightest. Early and late level mouse was shown similar color, but these levels were distinguished from control and active level mouse with the unaided eye. Permeability value of the efficacy of therapeutic intervention groups was presented in Table 3. The result of one way ANOVA in disease progression was presented in Table 4. Fig. 3 shows the change of Rheumatoid arthritis by staining CD31 at knee tissue, and it corresponds with Fig 4. Color of permeability map was darkening follow MTX treatment, but MTX does different do not shown definite permeability difference.

In case of this study, vascular permeability reflects angiogenesis and vascular structural changes the blood vessel wall by Rheumatoid arthritis. This fact was confirmed that Fig. 1 corresponds with Fig. 2 and Table 2. The result of this study indicates that control's blood vessel is not increase and stable, so permeability value is the lowest. Early RA model show a little angiogenesis, so permeability value increases than control. Active RA model has the highest permeability value because of active angiogenesis and increase gaps between endothelial cells. Late RA model has similar permeability value with early RA model, but meaning is different. Late RA model's tissue is hardening and atrophying, so permeability value decreases than active and similar early. In addition, this study show MTX help to change for the better, but little does difference was not shown definite change from vessel stain and permeability. Therefore, vascular permeability by using DCE-MRI and pharmacokinetic models can help know intuitively a region of lesion and progress of Rheumatoid arthritis.

Reference

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3. Liu, Z. et al. CII-DC-AdTRAIL cell gene therapy inhibits infiltration of CII-reactive T cells and CII-induced arthritis. Journal of Clinical Investigation 112, (2003).

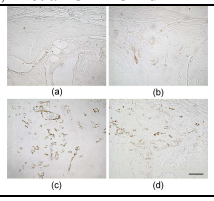

Figure 1. Vessel stain in ankle by anti-mouse CD 31, (a) control, (b) early RA model, (c) active RA model, (d) late RA model.

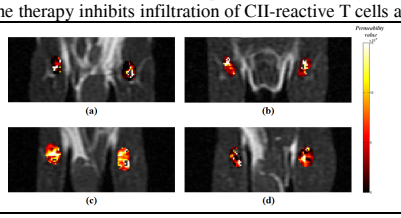

Figure 2. Color map of permeability around knee tissue of disease progression groups, (a) control, (b) early RA model, (c) active RA model, (d) late RA model.

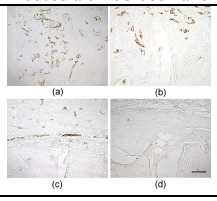

Figure 3. Vessel stain in ankle by anti-mouse CD 31, (a) active RA model, (b) MTX-low does, (c) MTX-high does, (d) control.

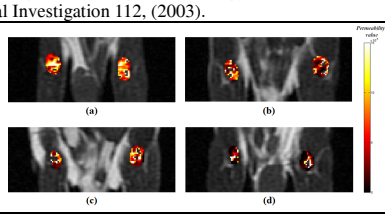

Figure 4. Color map of permeability around knee tissue of the efficacy of therapeutic intervention groups, (a) active RA model, (b) MTX-low does, (c) MTX-high does, (d) control.

Ration	Rheumatoid Arthritis Level			
	Control (N=5)	Early (N=5)	Active (N=5)	Late (N=5)
$K_{p\to t}/V_t$ ($\times 10^{-4}$ min^{-1})	1.419 ± 0.186	2.750 ± 0.255	5.533 ± 0.189	2.708 ± 0.253

Table 1. Permeability value of disease progression groups

RA Level	Control	Early	Active	Late
Control	-	0.03	0.00	0.04
Early	0.03	-	0.00	0.99
Active	0.00	0.00	-	0.00
Late	0.04	0.99	0.00	-

Table 2. p-value table for Permeability value of disease progression groups in One way ANOVA

Ration	Rheumatoid Arthritis Level			
	Active (N=5)	MTX-low does (N=5)	MTX-high does (N=5)	Control (N=5)
$K_{p\to t}/V_t$ ($\times 10^{-4}$ min^{-1})	5.533 ± 0.189	3.590 ± 0.393	3.002±0.390	1.419 ± 0.186

Table 3. Permeability value of the efficacy of therapeutic intervention groups

RA Level	Active	MTX-low does	MTX-high does	Control
Active	-	0.04	0.00	0.00
MTX-low does	0.04	-	0.44	0.01
MTX-high does	0.00	0.44	-	0.02
Control	0.00	0.01	0.02	-

Table 4. p-value table for Permeability value of the efficacy of therapeutic intervention groups in One way ANOVA