Intra-articular primatised anti-CD4: efficacy in resistant rheumatoid knees. A study of combined arthroscopy, magnetic resonance imaging, and histology


Abstract

Objectives—CD4+ T cells sustain the chronic synovial inflammatory response in rheumatoid arthritis (RA). SB-210396/CE 9.1 is an anti-CD4 monoclonal antibody that has documented efficacy in RA when given intravenously. This study aimed to establish the safety and efficacy of the intra-articular administration of SB-210396/CE 9.1 compared with placebo, examining its mode of action using a combined imaging approach of arthroscopy, magnetic resonance imaging (MRI), and histology.

Methods—Thirteen RA patients with active, resistant knee synovitis, were randomised to intra-articular injection of placebo (n=3), 0.4 mg (n=3) or 40 mg (n=7) of anti-CD4 after sequential dynamic gadolinium enhanced MRI, followed by same day arthroscopy and synovial membrane biopsy. Imaging and arthroscopic synovial membrane sampling were repeated at six weeks. This study used a unique region of interest (ROI) analysis mapping the MRI area analysed to the specific biopsy site identified arthroscopically, thus providing data for all three modalities at the same synovial membrane site.

Results—12 patients completed the study (one placebo treated patient refused further MRI). Arthroscopic improvement was observed in 0 of 2 placebo patients but in 10 of 10 patients receiving active drug (>20% in 6 of 10). Improvement in MRI was consistently observed in all patients of the 40 mg group but not in the other two groups. A reduction in SM CD4+ score was noted in the 40 mg group and in the 0.4 mg group. Strong correlations both before and after treatment, were identified between the three imaging modalities. Intra-articular delivery of SB-210396/CE 9.1 was well tolerated.

Conclusions—SB-210396/CE 9.1 is safe when administered by intra-articular injection. A trend toward efficacy was found by coordinated MRI, arthroscopic, and histological imaging, not seen in the placebo group. The value of ROI analysis was demonstrated.

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Rheumatoid arthritis (RA) is a chronic symmetrical polyarthritis characterised by persistent inflammation of the synovial membrane (SM) with characteristic mononuclear cell infiltration and lining layer hyperplasia. CD4+ T lymphocytes are believed to be important in RA SM interacting with other inflammatory cells including macrophages, synovial fibroblasts, and plasma cells. This role is supported by evidence that lymphocyte depletion, by thoracic duct drainage, total body irradiation or pharmacological manipulation is clinically efficacious in established RA.

A number of monoclonal antibodies (MAbs) directed against T cells have been administered in RA. Initially, murine and subsequently chimeric MAbs were delivered by the intravenous route. A recent review highlighted open studies demonstrating efficacy while double blind studies have been less convincing. A further study demonstrated a reduction in infiltrating T cells without clinical efficacy, suggesting that alternative mechanisms may also be important. Thus, doubts about the role of anti-CD4 have arisen, compounded by the absence of any objective measure of outcome, particularly as the acute phase response is not directly affected by anti-CD4 treatment.

The mainstay of treatment of inflamed joints is intra-articular (IA) injection of corticosteroids, benefit from which may be sustained for...
considerable periods. However, in certain cases relative resistance to such local treatment may develop. In such patients there is a need for an effective local treatment and such joints are suitable not only for novel interventions but are accessible for imaging thus offering the opportunity for definitive study of mode of action.

Conventional imaging of the joints, and histological examination of biopsy specimens from arthroscopy or a closed needle technique (Parker-Pearson needle), have previously been attempted, however limitations were noted.\(^{18,19}\) Needle arthroscopy is a safe and patient tolerable procedure permitting direct visualisation and biopsy of a specific region of interest (ROI) and semi-quantitative histological measures are well established.\(^{20,21}\) Magnetic resonance imaging (MRI) provides high quality digital images that can define cartilage and subchondral bone without exposure to ionising radiation.\(^{22,23}\) Its diagnostic capabilities have been compared with needle arthroscopy in the knee.\(^{24}\) Furthermore, the extent of synovial disease can be measured by scanning dynamically after the contrast administration. Quantitative analysis of dynamic Gd-DPTA enhanced MRI (DEMRI) can provide a measure of blood perfusion, capillary permeability, and extracellular volume all of which characterise the inflammatory process.\(^{19,14,25-27}\)

**Methods**

Thirteen RA patients (1987 American College of Rheumatology criteria) attending the Rheumatology clinic at Leeds General Infirmary, with active synovitis of the knee (pain, tenderness, effusion) that had proved resistant (<2 weeks improvement) to at least two IA corticosteroid injections were enrolled into this study. The study was approved by the local research ethics committee and written informed consent obtained from all subjects. All patients were receiving stable doses (>3 months) of oral medication: seven methotrexate, two sulphasalazine, one cyclosporin, one azathioprine; seven patients were receiving non-steroidal anti-inflammatory drugs and two subjects oral corticosteroids (<10 mg daily).

**STUDY DESIGN**

Patients were assessed on day −7, day 0 (dosing day), and days 3, 14, and 42 (study end). Clinical assessments by a single observer (RR), included measurement of knee circumference at midpoint of patella and physician assessment of disease activity in the signal knee. This was followed immediately by sequential imaging with dynamic Gd-DPTA enhanced MRI (DEMRI), followed within two hours by arthroscopy and synovial biopsy. Immediately after the arthroscopy 10 ml of SB-210396/CE 9.1 or placebo was administrated by slow IA injection at the tibiofemoral portal site. The physician performing the clinical assessment and giving the IA injection was blinded to the treatment and test results. Laboratory assessments including full blood count, biochemical profile, and C reactive protein were carried out at each imaging visit, and all investigations including DEMRI, arthroscopy and biopsy were repeated on day 42.

**MRI**

All MRI knee examinations were performed on a 1.5T Gyroscan ACS NT MR (Philips Medical Systems, the Netherlands) equipped with a quadrature knee coil. Patients were positioned supine with the signal knee placed within the knee coil and held in extension in the neutral position. After an initial localising scan multiple coronal and axial T1 weighted images were obtained to provide anatomical landmarks in the suprapatellar pouch (SPP) and tibiofemoral joint (TFJ), which were used to define a reproducible sagittal plane for quantitative measurements. This was perpendicular to two planes joining both the most (a) posterior margins localised axially, and (b) inferior margins localised coronally, of the femoral condyles. The quantitative measurements were derived from a dynamic T1 weighted gradient echo imaging sequence (TR/TE/flip angle 30/12/60°), which allowed the acquisition of 5 mm thick images every five seconds for a period of 200 seconds. Administration of Gd-DPTA was performed immediately after the first image of the series was obtained.\(^{28}\) Image analysis was performed using the Analyze biomedical image processing package\(^{29}\) and specially developed inhouse software. Two measurements of synovial disease activity were obtained using (a) magnitude and rate of Gd-DTPA uptake (b) enhancing synovial volume. Two regions of interest (ROI), 11.8 mm\(^2\) in area, were subsequently selected by the arthroscopist to correspond with the SPP and TFJ biopsy sites (fig 1). Signal intensity (SI) T1 curves were obtained from the ROIs for the entire series of dynamic images and normalised with respect to the

### Table 1 Patient characteristics by treatment group for study completers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0.4 mg</th>
<th>40 mg</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>3</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Female:male</td>
<td>2:1</td>
<td>6:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Median age in years (range)</td>
<td>72.3 (70–76)</td>
<td>62.6 (36–72)</td>
<td>68.0 (63–73)</td>
</tr>
<tr>
<td>Median disease duration in years (range)</td>
<td>11.3 (1–22)</td>
<td>11.4 (3–20)</td>
<td>13.3 (8–17)</td>
</tr>
<tr>
<td>Current DMARD use</td>
<td>3</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Current prednisolone use</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Baseline median knee circumference (cm) (range)</td>
<td>38.6 (37.6–39.5)</td>
<td>36.5 (36.1–38.9)</td>
<td>38.2 (35.4–41.0)</td>
</tr>
<tr>
<td>End median knee circumference (cm) (range)</td>
<td>38.4 (35.8–41.0)</td>
<td>37.1 (35.8–40.1)</td>
<td>38.6 (35.4–41.8)</td>
</tr>
<tr>
<td>Baseline median CRP (g/dl) (range)</td>
<td>8.5 (3.4–45.1)</td>
<td>27.5 (6.2–79.6)</td>
<td>66.1 (40.1–92.0)</td>
</tr>
<tr>
<td>End median CRP (g/dl) (range)</td>
<td>35.4 (15.0–52.2)</td>
<td>24.0 (8.4–102)</td>
<td>50.2 (8.4–92.0)</td>
</tr>
<tr>
<td>Intra-articular corticosteroid requirement at 18 months follow up</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
baseline (pre-contrast) SI. The maximal rate of SI enhancement (MRE) and the maximum SI enhancement (ME) was then calculated. A measure of the volume of enhancing synovial membrane was obtained by counting the pixels with greater than 50% ME. For each variable, the median value for the set of ROIs was found and the percentage change after treatment was then calculated. These changes were compared with the clinical and the arthroscopic findings.

**Figure 2** The percentage change of median dynamic enhanced (Gadolinium-DTPA) magnetic resonance imaging parameters over baseline with respect to: (A) maximum rate of normalised signal intensity enhancement (MRE) reflecting synovial capillary permeability; and (B) the maximum normalised signal intensity enhancement (ME) reflecting the perfusion and the volume of the extracellular fluid at the regions of interest and globally in the three treatment groups. (A) Deterioration in MRE is seen at both regions and globally in the placebo group. Ten per cent improvement is seen only at the tibiofemoral joint region in the 0.4 mg group. Improvement (up to 10%) is seen at both regions of interest and globally in the group treated with 40 mg of active drug. (B) Deterioration is seen at the suprapatellar region and globally in the placebo group. Ten per cent improvement is seen only at the tibiofemoral joint region in the 0.4 mg group. Improvement (up to 10%) is seen at both regions of interest and globally in the group treated with 40 mg of active drug.

**ARTHROSCOPY AND SYNOVIAL BIOPSY**

Needle arthroscopy with local anaesthetic (1% prilocaine) was performed immediately after MRI on days 0 and 42 at the day case unit, Chapel Allerton Hospital, Leeds. A Storz 2.7 mm diameter/30°/13 cm long arthroscope was introduced through standard portals. Images from an Endovision camera, using an halogen light source, were displayed on a 14” Sony colour monitor. The arthroscopic findings and SM sampling sites were reported on a graphic assessment form and recorded on super-VHS videotape. Systematic inspection of the SPP and TFJ compartments was performed, grading hyperaemia (0–1), granulation (0–1) or villous hypertrophy (0–2). In addition, an overall impression of the synovial inflammation was recorded on a 100 mm visual analogue scale. Synovial biopsy specimens (4–6 mm² in size) from sites in the sagittal plane corresponding to that used for MRI acquisition and to represent maximal and minimal inflammation were taken under direct vision using biopsy forceps. Joint irrigation was completed to a minimum of 1000 ml 0.9% saline and 10 ml of study drug or placebo was then slowly injected into the knee. The wounds were dressed with Steristrips and Primapore and crepe bandage applied for 24 hours. The patients were rested and observed for 60 minutes before discharge home. The post-treatment arthroscopy was conducted identically with repeat SM sampling from synovium within the imaging axis, immediately adjacent to the sites of pre-treatment biopsy.

**IMMUNOHISTOLOGY**

One biopsy specimen from each site was fixed in 10% formaldehyde for conventional histological preparation with haematoxylin and eosin, and one sample from each site was embedded in Bright’s OCT, snap frozen at −70°C and stored in a refrigerator at −80°C until sectioned. Serial sections 5 µm thick were cut, mounted on glass slides, fixed in acetone at room temperature, and air dried. A routine three stage immunoperoxidase staining technique was used with monoclonal antibodies to CD3, CD4 (OKT4), CD8, CD20, CD68, and MHC class II. Incubations were carried out at room temperature, primary antisera were diluted in phosphate buffered serum (PBS) with 1% (weight/volume) bovine serum albumin (BSA). The horseradish peroxidase (HRP) conjugated antibodies were diluted in 1% PBS-BSA with 10% (volume/volume) normal human serum as blocking serum. Endogenous peroxidase activity was inhibited using 0.1% sodium azide and 0.3% hydrogen peroxide in PBS. All sections were scored independently by two observers (AWB and DJV), before the study was unblinded, using a recognised 5 point scale for semiquantitative scoring, a score of 0 = minimal infiltration, a score of 4 = numerous inflammatory cells. In addition, each SM sample was assigned a score for lining layer hyperplasia (LLH) (0 = 1–2 cell layers, 1 = 3–4 cell layers, 2 = 5–6 cell layers, 3 = ≥7 cell layers). Positive and negative staining controls were used throughout.
In view of the small numbers of patients in each group median values were calculated for all imaging parameters, differences before and after were examined using Wilcoxon paired test and correlations with the Spearman rank test. Significance was defined at the p < 0.05 level.

Results

There were three male and 10 female subjects aged between 35–76 years (mean 66) with a mean disease duration of 12.4 years (range 2–29). Twelve patients were seropositive for rheumatoid factor. One placebo group patient did not complete the study because of refusal to undergo follow up MRI resulting from claustrophobia. The patients in the low dose treatment group had a higher mean age than the other groups, however disease duration was comparable. One patient in each active treatment group was receiving oral prednisolone treatment and only one participant (in the 40 mg cohort) was not receiving concomitant DMARD treatment. One patient receiving placebo and three receiving 40 mg active drug experienced injection site pain, however no serious adverse events were recorded with follow up at 18 months. No significant difference was observed in knee circumference or acute phase protein response. The mean C reactive protein (g/dl) showed no significant improvement in any group over the study. In addition, no statistically significant improvement was observed in the knee circumference or physician assessment of knee synovitis over the study period, although the latter showed a slight improvement in all seven patients who received high dose treatment. Clinical follow up now extends to 18 months in this group and nine patients have not required any further local injection therapy in this period (table 1).

Arthroscopy

Table 1 shows the arthroscopic scores for synovitis as measured with the VAS before and after treatment. The VAS for synovitis deteriorated in the two placebo patients while the actual scores and the median values in all patients receiving active treatment showed an improvement. Taking improvement of 20% or more as significant, two of three patients receiving 0.4 mg and four of seven of the 40 mg group reached this level. Analysis of the median improvement in the treated patients overall showed there was a 27 mm (42%) and 22 mm (27%) change in the 0.4 mg and the 40 mg group respectively. Synovial inflammation was also subjectively graded according to a number of visual features including granularity, vascularity, and villous hypertrophy. There was no significant trend in this assessment between the patient groups or in relation to treatment.

Table 2 Arthroscopic VAS assessments (mm), observer scoring overall synovitis before and after dosing with intra-articular primatised anti-CD4 monoclonal antibody

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Arthroscopic VAS for synovitis before dose</th>
<th>Arthroscopic VAS for synovitis after dose</th>
<th>Difference in scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo 0 mg</td>
<td>69</td>
<td>76</td>
<td>7</td>
</tr>
<tr>
<td>median</td>
<td>68</td>
<td>73</td>
<td>-5</td>
</tr>
<tr>
<td>0.4 mg</td>
<td>64</td>
<td>60</td>
<td>4</td>
</tr>
<tr>
<td>median</td>
<td>64</td>
<td>48</td>
<td>27</td>
</tr>
<tr>
<td>40 mg</td>
<td>89</td>
<td>71</td>
<td>28</td>
</tr>
<tr>
<td>median</td>
<td>80</td>
<td>58</td>
<td>22</td>
</tr>
<tr>
<td>76</td>
<td>76</td>
<td>47</td>
<td>29</td>
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<td>77</td>
<td>77</td>
<td>63</td>
<td>14</td>
</tr>
<tr>
<td>83</td>
<td>83</td>
<td>73</td>
<td>10</td>
</tr>
<tr>
<td>median</td>
<td>80</td>
<td>61</td>
<td>22</td>
</tr>
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of MRE at the SPP and the TFJ (fig 2A and fig 3). On analysis of a global score representing the change in MRE at both ROIs in the three groups there was a dose response effect, although this did not reach statistical significance.

A change in ME before and after treatment was seen in patients who received active drug. The % change in median ME (fig 2B), showed a similar pattern to the change in MRE, with improvement at both ROIs (globally) seen only in those patients receiving the high dose while the 0.4 mg group showed a small response at the TFJ ROI but not at the SPP ROI. In the 40 mg group, ME at the TFJ improved by 17.6% and at the SPP ROI by 16% over the study period. The synovial volume measurements did not change significantly over the course of the study.

**HISTOLOGICAL ASSESSMENT**

There was an increase in the median scores for SM lining layer hyperplasia and CD4 cells in both placebo patients during the study (table 2). In contrast, the lining layer score showed a decrease in both treatment groups. This was most marked in the low dose group, in which two of three patients showed a noticeable improvement followed by the 40 mg dose group, in which five of seven patients either showed no change or a slight improvement. The immunohistological staining showed changes in the CD4 score with improvement in the active groups before (fig 4A) and after (fig 4B) treatment while the placebo group deteriorated. Overall, the global CD4 score showed a reduction by 30%, representing an improvement in the group who received 40 mg of active drug while increases of 15% and 10% were seen in the 0.4 mg group and in the placebo group, respectively (fig 5). Analysis of CD3, CD8, CD20, CD68, MHC class II revealed no significant change.

Immunophenotyping of peripheral blood lymphocytes performed at baseline and repeated at the end of the study showed a marginal reduction in numbers of circulating CD3+/CD4+/CD8- cells in both treatment groups and a rise in the placebo group (data not shown).

**CORRELATIONS BETWEEN IMAGING TECHNIQUES**

Several statistically significant correlations were observed in this study between the imaging modalities examined and these held true across both time points (table 3). The most significant correlations were observed between the MRE at the SPP ROI and the arthroscopic VAS for synovitis \( (r=0.77; \ p=0.003) \) and between the MRE and immunohistological CD4 score, globally \( (r=0.70; \ p=0.011) \). Significant correlations were also seen between the arthroscopic VAS for synovitis and the histological SM LLH global score \( (r=0.59; \ p=0.042) \), which in turn also correlated with the CD4 global score. These correlations were calculated for the ROIs selected at arthroscopy, biopsied under direct visual inspection and subsequently mapped on to the MR image.
Table 3 Global CD4 counts and lining layer hyperplasia scores before and after dosing with intra-articular primatised anti-CD4 monoclonal antibody

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>CD4 before dose</th>
<th>CD4 after dose</th>
<th>Difference in scores</th>
<th>Hyperplasia before dose</th>
<th>Hyperplasia after dose</th>
<th>Difference in scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 mg</td>
<td>7</td>
<td>8</td>
<td>-1</td>
<td>2</td>
<td>4</td>
<td>-2</td>
</tr>
<tr>
<td>3 mg</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>-2</td>
</tr>
<tr>
<td>Median</td>
<td>5.5</td>
<td>1</td>
<td>-0.5</td>
<td>1</td>
<td>3</td>
<td>-2</td>
</tr>
<tr>
<td>0.4 mg</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>0.5</td>
<td>3.5</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>-1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>2.5</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>3.5</td>
<td>1.5</td>
<td></td>
</tr>
</tbody>
</table>

Table 4 Correlations between imaging modalities, including arthroscopic assessment, region of interest magnetic resonance analysis, and immunohistochemistry

<table>
<thead>
<tr>
<th>Correlations</th>
<th>r value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS and Y - SPP region</td>
<td>0.774</td>
<td>0.003</td>
</tr>
<tr>
<td>Y - CD4</td>
<td>0.7022</td>
<td>0.011</td>
</tr>
<tr>
<td>VAS and CD4</td>
<td>0.5694</td>
<td>0.053*</td>
</tr>
<tr>
<td>VAS and hyperplasia - SPP region</td>
<td>0.5924</td>
<td>0.042</td>
</tr>
<tr>
<td>VAS and hyperplasia</td>
<td>0.6952</td>
<td>0.012</td>
</tr>
<tr>
<td>CD4 and hyperplasia</td>
<td>0.6291</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Statistical significance at the 5% level using Spearman’s correlation. *Borderline statistically significant.

Four patients (three from the 40 mg group and one placebo) experienced pain at the injection site on drug administration, no further sequelae were identified. One patient from each treatment group also experienced mild worsening of synovitis and swelling in the target knee, which resolved fully by the final study visit and did not require additional treatment.

Discussion

This double blind study showed that IA administration of SB-210396/CE 9.1, a primatised anti-CD4 MAAb, at 40 mg is safe and produces a trend toward improvement in MRI, arthroscopic, and histological outcome measures. Significant correlations were demonstrated between the three imaging modalities studied, all of which were carried out by independent observers blinded to the other results. This provides internal consistency and strong support for this approach as a means of studying the mode of action of drugs. Importantly, the correlation between histology and MRI was significant only with those ROIs that corresponded to the site from which the biopsy specimen was taken. This highlights the patchy nature of disease and emphasises the importance of coordinated imaging with direct visualisation of biopsy and MRI.

Arthroscopic synovitis VAS improved consistently in all patients receiving active treatment while two placebo patients showed deterioration. Improvements were small, however in two of three low dose group and four of seven high dose group patients it was >20%. A reduction in the median SM LLH with histological assessment occurred in all patients receiving active treatment while in the placebo patients it increased. Additionally, the CD4 scores decreased in the high dose group and improved in two of three low dose group patients with deterioration in the placebo group. There are a number of possible explanations for this apparent reduction in the number of CD4+ cells, which may represent a reduction in T cells or macrophages, or both, including fewer cells entering the joint, prolonged coating of cells or increased clearance from the SM.

Time-dependent change of MRI SI after intravenous administration of Gd-DPTA is influenced by the local tissue properties such as perfusion, extracellular fluid volume, and capillary permeability. Descriptive variables such as ME and MRE reflect a combination of physiological variables, however, ME depends mainly on local Gd-DPTA availability (perfusion and volume of extracellular fluid) whereas MRE reflects capillary permeability. Analysis of these DEMRI variables at both specific ROIs showed improvement in the high dose group compared with placebo in a dose response trend, although synovial volumes did not change significantly. This is in contrast with previous findings by Ostergaard et al. who showed a good correlation with measurement of total enhancing volume. In that work, regions were defined interactively introducing possible bias, additionally percentage enhancement was not calculated.

In addition to the changes within each imaging modality several strong correlations were observed between sequential same day DEMRI measures, arthroscopic VAS for synovitis, and synovial immunohistochemistry, specifically between MRE, synovitis VAS, and CD4 score. The validity of these correlations is supported by the fact that they were consistent at two separate time points—before and after treatment. Two previous studies attempted to correlate dynamic MR with SM histology showing correlation between synovial volume and inflammation. In a further study of anterior knee pain, some correlation between clinical, arthroscopic, and MRI features was described. Limitations of all these studies were long MR acquisition intervals and/or closed needle biopsy with mismatch to MR analysis and reduced sensitivity, furthermore in these studies, there was no immunohistochemical staining.

This is the first study to examine a therapeutic intervention simultaneously with arthroscopic assessment, histological assessment, and MRI. The dynamic MR sequences with high temporal resolution continuing into plateau phase, provides a more accurate measure of tissue microcirculation. In addition, the time lapse between MR scan and arthroscopy was minimal (<2 hours) and SM biopsy specimens were obtained by direct visualisation. Previous intervention studies using SM examination as an outcome are limited, one study of gold treated patients correlated clinical improvement with reduced inflammatory cell infiltration. This study was limited by a high rate of failed biopsy, a problem overcome in this study by the use of arthroscopic SM sampling.
Early studies of anti-CD4 treatment used murine, depleting MAb and subsequently chimeric, non-depleting MAbs. SB-210396/CE 9.1 is a chimeric primate/human MAb directed to surface expressed CD4. Phase II studies suggest it has good clinical efficacy when administered intravenously in patients with established RA. Intravenous SB-210396/CE 9.1 achieved good levels in the peripheral circulation and the side effect profile is good. The intra-articular concentration however may be sub-optimal, so this study looks at the question: is direct delivery of anti-CD4 MAb to the primary site of disease—the synovium—both safe and efficacious? Of 11 previous studies of IV anti-CD4, only one showed statistical clinical improvement and only three were blind and placebo controlled. Results have been disappointing: indicating the key putative role for CD4+ T cells in RA and the dramatic clinical response with anti-TNF treatment, however the subjects had end stage disease and therefore less capacity for improvement. In contrast, the study of intravenous SB-210396/CE 9.1 in established refractory RA showed that this MAb was efficacious. The study of intravenous chimeric murine/human antibody (cM-T412) in short disease duration patients (<1.5 years) showed little clinical benefit, but a decreased cellular inflammation and adhesion molecule expression after four weeks. In contrast, the study of anti-TNF MAb (cA2) resulted in clinical benefit and a reduction in SM cellularity but no correlation between the two. The management of resistant knee synovitis in RA remains a significant clinical problem. In the event of lack of efficacy of IA corticosteroids, alternative treatment options are limited. Manufacture of DMARD dose may not be possible because of toxicity, side effects and even if possible may result in early day delay in clinical response. This study shows that IA administration of SB-210396/CE 9.1 is safe and well tolerated by patients and it suggests possible efficacy of at least a dose of 40 mg IA SB-210396/CE 9.1, (possibly at 0.4 mg), in RA patients with resistant knee synovitis. The regimen of combined imaging in assessing outcome using dynamic MRI, arthroscopy, and SM biopsy has demonstrated significant correlations in a number of parameters. This study confirms the feasibility and validity of a combined imaging approach, suggesting this is a useful method for mode of action studies for therapeutic agents in RA treatment. It is possible that it will also result in new therapeutic approach for locally resistant joints.

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References:


Historical images
Series editors: W Grassi, C Cervini

Figure 15 Enchondroma of the humerus.
Intra-articular primatised anti-CD4: efficacy in resistant rheumatoid knees. A study of combined arthroscopy, magnetic resonance imaging, and histology


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