Sulesomab (LeukoScan) imaging in joint prostheses

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Introduction
The number of prosthetic joint replacement has increased steadily over the last decade in the UK. From April 2008 to March 2009, there have been 29,146 hip prostheses and 33,722 knee prostheses performed in 118 NHS Trusts within England and Wales. A prosthetic joint replacement is a well-established method in the management of joint pain as well as improving joint mobility. Nonetheless, prosthetic joints may fail due to aseptic loosening, infection, dislocation and fracture of the prosthesis or bone. Infection and aseptic loosening account for significant number of failures.

The symptoms and clinical findings are similar and differentiating between the two can be difficult. Peri-prosthetic infection following total hip or knee arthroplasty is associated with significant costs and morbidity. The infection rate following primary implantation and revision surgery is high, 1% and 3% for hip prostheses and 2% and 5% for knee prostheses, respectively. With the increasing number of joint prostheses replacements, the rate of infection will be significant, thus making diagnosis of peri-prosthetic infection essential.

The management of infected joint prosthesis normally involved prolonged antimicrobial therapy with one or two step prosthesis revision, whereas aseptic loosening normally requires only a single revision arthroplasty.

The diagnosis of septic loosening of joint prostheses is difficult through clinical signs and symptoms, laboratory tests or plain radiography. The use of joint aspiration is insensitive and non-specific. Imaging remains an ideal method in diagnosing peri-prosthetic infection. Cross-sectional imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) have problems with artefacts from the presence of metallic prosthesis. Radionuclide imaging on the other hand is less affected by artifacts from the presence of metallic prosthesis, thus much more appropriate as an imaging modality for investigating peri-prosthetic infection.

Radionuclide imaging for the investigation of infected joint prosthesis includes bone scintigraphy, gallium scintigraphy, radionuclide imaging in joint prostheses and fluorodeoxyglucose joint prosthesis which includes bone scintigraphy, gallium scintigraphy. Cross-sectional imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) have problems with artefacts from the presence of metallic prosthesis. Radionuclide imaging on the other hand is less affected by artifacts from the presence of metallic prosthesis, thus much more appropriate as an imaging modality for investigating peri-prosthetic infection.

Radionuclide imaging for the investigation of infected joint prosthesis includes bone scintigraphy, gallium scintigraphy, radionuclide imaging in joint prostheses and fluorodeoxyglucose positron emission tomography (FDG-PET). Radionuclide imaging in joint prostheses involves prolonged antimicrobial therapy with one or two step prosthesis revision, whereas aseptic loosening normally requires only a single revision arthroplasty.

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Radionuclide imaging in joint prostheses has been established as the gold standard for imaging of infected joint prosthesis. Unfortunately, there is the problem of in vitro handling of blood, thus making it time-consuming and exposing radiopharmacy personnel to the risk of blood-borne infection. Both bone and gallium scintigraphy have low accuracy and FDG-PET imaging is expensive and not widely available for this indication.

Radionuclide imaging in joint prostheses has been extensively investigated and have proven to be an excellent radionuclide tracer for the imaging of infected joint prosthesis. This is due to the fact that these radiolabelled monoclonal antibodies or antibody fragments directly target leukocyte antigens or receptor in vivo and enabled assessment of the concentration of granulocytes in the inflamed tissue surrounding the prosthesis.

There are currently two radiolabelled monoclonal antibodies which are used in clinical practice. One is a murine immunoglobulin of IgG1 isotype (Beulosemab) which specifically binds to the non-specific cross-reacting antigen-95 (NCA-95) that is expressed at the cell membrane of granulocytes and granulocyte-monocytic leucocytes. The other is a small murine monoclonal antibody fragment (Fab') of the immunoglobulin G antibody (Sulesomab) against the normal cross-reacting antigen-90 (NCA-90) which is present on the surface of virtually all neutrophils. This article will focus on the use of sulesomab in radionuclide imaging for the investigation of peri-prosthetic infection.

Sulesomab characteristics
Sulesomab (LeukoScan, Immunomedics Inc, Morris Plains, NJ, USA) Fab' monoclonal antibody is produced from a hybridoma developed by fusion of murine myeloma cells with spleen lymphocytes obtained from a mouse immunised with carcinoembryonic antigen (CEA). As described above, sulesomab will react strongly with NCA-90. In activated granulocytes, which occur during infection, there is an overexpression of the NCA-90 antigen on the surface of these granulocytes. Therefore, sulesomab will have a greater binding affinity to activated granulocytes as opposed to quiescent granulocytes. This will target the site of the infection whereby most of the activated granulocytes will have migrated to. This also explains the fact that sulesomab scintigraphy is preferred in the detection of acute infection, which is mainly mediated by granulocytes as opposed to chronic infections, which is mediated through a different mechanism.

Although the use of sulesomab removes the need for in vitro labelling blood products, thus reducing the risk of exposure to blood borne infections to radiopharmacy personnel, there is the theoretical risk of an immune reaction. This is due to the fact that sulesomab is a murine monoclonal antibody fragment (Fab'), thus there is a possibility that the human immune system might perceive it as foreign and mount an immune response against it, producing human anti-mouse antibodies (HAMA).

Nonetheless, the risk of immunotoxicity of sulesomab is minimal as Fab' cannot activate complement or effect antibody-dependent cytotoxicity. This is because Fab' is a monovalent and therefore cross-linking of antigen on cell surface is not possible. Furthermore, the low dose of Fab' reduces the risk of any pharmacological effect on granulocyte function.

Harwood and co-workers showed that, in a cohort of 150 patients, none died or dropped out of the study due to adverse reactions. They have also shown that none of the 96 patients who had both pre-injection and at least one post-injection HAMA determination (1-4 months after IV sulesomab injection) developed a positive HAMA response or a positive boost response (an increase in HAMA titre in those with HAMA present at baseline) to the Fab'. Becker and co-workers also demonstrated similar results whereby in 13 patients tested for HAMA before and up to four months following sulesomab administration, none had an elevation in HAMA. Both studies have demonstrated that sulesomab is safe to be used as a radionuclide tracer for imaging.

Sulesomab protocols
There is some variation to the methods of scintigraphic acquisition protocols and image interpretation performed in different centres as demonstrated in the various studies.
Sulesomab scintigraphy diagnostic effectiveness

There have been numerous studies performed using sulesomab to assess its reliability and diagnostic accuracy in detecting peri-prosthetic infection. The findings of the use of sulesomab scintigraphy in the investigation of peri-prosthetic infection has been summarised in Table 1.

Pakos and co-workers performed a meta-analysis of diagnostic studies regarding the accuracy of antigranulocyte scintigraphy (AGS) with monoclonal antibodies in the identification of prosthesis infection after total hip or knee arthroplasty. They have included both sulesomab and beslesomab studies within the meta-analysis. They found a range of sensitivity and specificity of 57%-100% and 65%-100% respectively among all the studies. The meta-analysis calculated an overall sensitivity and specificity of 85% and 80% respectively. A further subgroup analysis for only sulesomab studies showed similar sensitivities and specificities of 83% and 81% respectively.

Rubello and co-workers have recently published data on the use of sulesomab scintigraphy in both hip and knee prostheses assessment for infection using early (4 hour) and late (20-24 hour) images with a four-step scale visual analysis. They have also performed semi-quantitative region of interest (ROI) analysis using ROI method. They reported sensitivity, specificity and accuracy of 100%, 100% and 100% respectively for severe infection, 88%, 90% and 90% respectively for moderate infection and 72%, 66% and 85% respectively for mild infection.

There is limited information in the literature on the use of SPECT or SPECT-CT imaging for peri-prosthetic infection with sulesomab scintigraphy. Rubello and co-workers mentioned that SPECT images did not add significant information in respect to sensitivity and specificity to their study. However, they have only performed SPECT acquisition in a selected number of patients. In our experience, we found SPECT-CT can be helpful in certain patients and enables better localisation of the site of infection.

Hip and knee prostheses are the most frequently investigated prosthetic joints for peri-prosthetic infection. A few studies, including a meta-analysis, have shown that the use of sulesomab scintigraphy has a higher sensitivity, specificity and diagnostic accuracy for knee joint prostheses.

All the studies have demonstrated a relatively high sensitivity and negative predictive value for the use on sulesomab scintigraphy in the detection of peri-prosthetic infection. This indicates that sulesomab scintigraphy may have a better role in excluding peri-prosthetic infection. There have been advocates for the use of bone scintigraphy in conjunction with sulesomab scintigraphy. A suggestion of concomitant use of marrow imaging may help improve the diagnostic accuracy but no such studies have yet been published.

Clinical example

Within our local institution, we have found sulesomab scintigraphy to be helpful in excluding infection in bone scintigraphy of joint prostheses that are inconclusive. An example is a 76-year-old gentleman, who had a right hip replacement in 2003, developed persistent pain in the right hip more than a year post-operatively. The two phase bone scintigraphy showed increased activity surrounding the femoral component of the right hip prosthesis on both blood pool and delayed images (Figure 1). A subsequent sulesomab scintigraphy showed no increase activity at the corresponding site (Figure 2). Further aspirate from the right hip showed no growth on culture and histology showed no signs of inflammation or infection. This confirms that the pain from the right hip was due to aseptic looseness rather than infected prosthetic joint.

### TABLE 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>Positive predictive value (PPV)</th>
<th>Negative predictive value (NPV)</th>
</tr>
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<tbody>
<tr>
<td>Ryan, 2002</td>
<td>85%</td>
<td>77%</td>
<td>NR*</td>
<td>58%</td>
<td>93%</td>
</tr>
<tr>
<td>Ivancevic et al, 2002</td>
<td>100%</td>
<td>58%</td>
<td>73%</td>
<td>57%</td>
<td>100%</td>
</tr>
<tr>
<td>Vicente et al, 2004</td>
<td>80%</td>
<td>89%</td>
<td>87%</td>
<td>63%</td>
<td>91%</td>
</tr>
<tr>
<td>Von Rothenburg et al, 2004</td>
<td>93%</td>
<td>65%</td>
<td>NR+</td>
<td>63%</td>
<td>94%</td>
</tr>
<tr>
<td>Iyengar et al, 2005</td>
<td>91%</td>
<td>81%</td>
<td>84%</td>
<td>67%</td>
<td>96%</td>
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* Not recorded in the study findings.

The standard dose of sulesomab administration is 750MBq (20mCi). This is also the diagnostic reference level documented by the Administration of Radioactive Substances Committee (ARSC) in its guidance notes. The images are normally acquired between 4-6 hours post-injection of sulesomab intravenously with additional images obtained at 20-24 hours post-injection. Most centres will only perform planar scintigraphy of the suspected infective site. There is an option of performing additional single photon emission computed tomography (SPECT) acquisition with or without computed tomography (CT). Majority of the interpretation is based purely on visual analysis of the images.

In our department, we normally performed sulesomab scintigraphy as a suspected prosthetic joint infection with a minimum duration of 12 months following the surgical prosthetic joint implantation. This is to reduce the number of false positive results due to post-surgical inflammatory changes. All patients due for sulesomab scintigraphy normally have a prior dual-phase bone scintigraphy.

All sulesomab administration is performed with slow intravenous injection over 30 seconds and monitoring of heart rate and blood pressure due to the risk of hypereosinophilia reaction. We do not normally repeat sulesomab scintigraphy on patients who had previous exposure. If this is considered, HAMA titres will be measured prior to the repeat study.

We normally acquire planar images of the suspected site of infection 4 hours post-injection. If the planar images appear inconclusive, we will proceed to perform SPECT or SPECT-CT acquisition to help with image interpretation and reporting.

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Conclusion
A number of conclusions can be drawn from all the studies:

1. Sulesomab is a safe tracer for radionuclide imaging with no documented HAMA reaction following re-injection in a limited number of patients.

2. Sulesomab scintigraphy should be performed in patients investigated for peri-prosthetic infection after 12 months of surgical procedure to reduce the number of false positives. However, if sulesomab scintigraphy is performed on prosthetic joints within 12 months of surgery, additional 24-hour images with semi-quantitative ROI may help reduce false positives.

3. Sulesomab scintigraphy is best used to exclude infection in joint prostheses following an inconclusive bone scintigraphy given the relatively high negative predictive value.

4. Sulesomab scintigraphy can be employed in patients either on or off antibiotics with similar sensitivity and specificity for detection on prosthetic joint infection.

5. The use of four-hour and 24-hour planar images with semi-quantitative ROI analysis appears to yield the best diagnostic accuracy.

When the pitfalls for sulesomab scintigraphy are avoided, this technique is a very useful addition to the imaging techniques in detecting prosthetic joint infections. Sulesomab scintigraphy has a definite role in the diagnosis of peri-prosthetic infections.

References


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19. Sulesomab scintigraphy can be employed in patients either on or off antibiotics with similar sensitivity and specificity for detection on prosthetic joint infection.

FIGURE 1
Both blood pool and delayed images of the pelvis and both hips showed increased tracer accumulation and uptake surrounding the mid to distal part of the femoral component of the right hip prosthesis.

FIGURE 2
The four-hour post-injection sulesomab images of the pelvis and both hips do not show any increase tracer uptake in the corresponding region around the mid to distal part of the femoral component of the right hip prosthesis.