Osteomyelitis: antigranulocyte scintigraphy with 99mTc radiolabeled monoclonal antibodies for diagnosis. Meta-analysis

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CRD summary
This review assessed the diagnostic accuracy of antigranulocyte scintigraphy with monoclonal antibodies for the diagnosis of osteomyelitis. The authors concluded that the sensitivity was 81% and the specificity 77%, so the method, while useful, cannot completely replace established methods. Although the review was rigorously conducted, the conclusions represent an over-interpretation of the results from a relatively small number of patients and may not be reliable.

Authors' objectives
To assess the sensitivity and specificity of antigranulocyte scintigraphy with monoclonal antibodies (MoAbs) in the diagnosis of osteomyelitis in different patient groups and clinical settings.

Searching
MEDLINE and EMBASE were searched to June 2006; the search terms were reported. Only published studies were eligible for inclusion in the review but there were no language restrictions. References were also checked.

Study selection
Diagnostic accuracy studies with at least 10 patients were eligible for inclusion. Eligible studies assessed the diagnostic performance of antigranulocyte scintigraphy with any MoAb against any reported reference standard(s). The reference standard used in the studies was accepted. The included studies used sulesomab, BW 250/180 or faneolosomab MoAbs. Interpretation was quantitative, semi-quantitative or qualitative. The reference standards in the included studies were one or more of cell culture, clinical follow-up, histologic examination, and radiologic examination including conventional radiography, ultrasonography, magnetic resonance imaging and computerised tomography. Studies of participants with suspected osteomyelitis were eligible for inclusion; this included both those who were eventually diagnosed with osteomyelitis and those who were not. The included studies recruited patients with both peripheral and axial osteomyelitis, and with both acute and chronic disease. No inclusion criteria for the outcomes were stated. The included studies reported true and false negatives and positives.

Two reviewers assessed studies for inclusion in the review. Any disagreements were resolved through consensus.

Assessment of study quality
The validity of the studies was assessed using the Quality Assessment of Studies of Diagnostic Accuracy included in Systematic Reviews (QUADAS) tool. It appears that three reviewers independently assessed the studies for validity, with any discrepancies resolved through consensus or arbitration by a fourth reviewer.

Data extraction
Data on true positives, false positives, true negatives and false negatives were extracted. Data on subgroups for type of osteomyelitis (acute versus chronic), location (axial versus peripheral) and reference standard employed were also extracted. Sensitivity and specificity were calculated with 95% confidence intervals (CIs), and the diagnostic log odds ratio (DOR) was calculated.

Three reviewers independently extracted the data. Any discrepancies were resolved through consensus or arbitration by a fourth reviewer.

Methods of synthesis
Study sensitivities and specificities were pooled using a random-effects model. Statistical heterogeneity was assessed using the Fisher exact test. The DORs were pooled using a random-effects calculation. The positive and negative
likelihood ratios (LRs) with 95% CIs were estimated using random-effects calculations, and statistical heterogeneity between studies was assessed using the Q statistic. Subgroup analyses were based on type and localisation of osteomyelitis, study design, type of MoAb, time of antigranulocyte scintigraphy after injection, methods used for interpretation of scintigraphy and blinding. In addition, sensitivity analyses of the impact of studies with a single reference standard method were conducted. Both weighted (by inverse variance) and unweighted summary receiver operating characteristic (ROC) curves were constructed using the Moses and Littenberg model. A hierarchical summary ROC analysis was also used. Publication bias was assessed by examining asymmetry in a funnel plot of the log odds ratio against the inverse of the effective sample size.

Results of the review
Nineteen studies (n=683, total of 714 examinations) were included in the review.

The validity of the included studies was variable, with only 6 studies reporting blinding of the assessors and 4 studies reporting data on patient exclusions.

There was no evidence of publication bias, as assessed by funnel plot asymmetry (p=0.26).

The summary estimate of sensitivity was 81% (95% CI: 70, 88) and the summary estimate of specificity was 77% (95% CI: 66, 86). Both estimates showed statistically significant heterogeneity between the studies (p<0.001 in both cases).

Paired results from the weighted and unweighted ROC curves were also reported.

The weighted positive LR was 3.02 (95% CI: 2.07, 4.42) and the weighted negative LR was 0.26 (95% CI: 0.17, 0.39). There was statistically significant heterogeneity between the studies for both statistics. Joint estimation of the values using a hierarchic ROC analysis gave values of 4.08 (95% CI: 3.36, 4.80) and 0.34 (95% CI: 0.10, 0.58), respectively.

The pooled DOR was 19.4 (95% CI: 9.1, 41.3).

The negative LR was significantly lower for the diagnosis of axial versus peripheral lesions (p=0.001). The results of other subgroup analyses were also reported in detail; numbers in subgroups were small.

Authors’ conclusions
Antigranulocyte scintigraphy with MoAbs has a sensitivity of 81% and a specificity of 77% in the diagnosis of osteomyelitis.

CRD commentary
The review question and the inclusion criteria were clear. The authors searched two relevant databases, but restricting the review to published studies might have increased the possibility that some relevant studies were not included in the review. However, the authors reported that they assessed publication bias and found no evidence of it. The authors reported using appropriate methodology to limit bias and error in all stages of the review, and they conducted an appropriate validity assessment, which was used to inform the statistical synthesis. A number of methods were employed to statistically combine the studies and to investigate heterogeneity, of which some were more informative than others. Given the wide ranges of sensitivities and specificities of the included studies, the presentation of pooled estimates for these variables as conclusions of the review, to the exclusion of other more informative data, represents an over-interpretation of the results and cannot be considered reliable.

Implications of the review for practice and research
Practice: The authors stated that while MoAbs can be used as a major diagnostic method in patients suspected of having osteomyelitis, they cannot completely replace histologic examination and cell culture.

Research: The authors did not state any implications for further research.

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