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Ultrasound to Guide Treatment Decisions in Rheumatoid Arthritis

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INTRODUCTION and OBJECTIVE

Ultrasound (US) detects synovitis more accurately than clinical examination in people with rheumatoid arthritis (RA). This review aimed to investigate the use of US, compared to clinical examination alone, in treatment strategies for RA, and to estimate its potential to be cost-effective in making treatment decisions.

METHODS

Systematic reviews were conducted of studies where US-detected synovitis had been used to inform prediction of treatment response or treatment tapering when compared with clinical examination assessed synovitis; and to identify papers assessing the cost-effectiveness of US to monitor synovitis. To inform the model, a systematic search sought studies of tapering RA treatment regardless of the involvement of US. The following electronic databases were searched from inception to October 2015 as part of a larger project[1]: MEDLINE AND MEDLINE In-Process Citations Ovid; EMBASE Ovid; Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials; Health Technology Assessment Database; Database of Abstracts of Reviews of Effects; NHS Economic Evaluation Database; Science Citation Index Expanded; Science Citation Index and Conference Proceedings Index; Clinical Trials.gov; European League Against Rheumatism Abstract Archive searched via Web of Science; American College of Rheumatology and Association of Rheumatology Health Professionals searched via Web of Science; OMERACT conference abstracts searched via Web of Science. The full search strategy and details of the full project will be available from the HTA website in the future.[1]

A model was constructed to investigate the potential cost-effectiveness of US in i) selecting patients suitable for treatment tapering; ii) avoiding treatment escalation.

RESULTS

Searches of electronic databases from a larger project[1] yielded 2724 results. Following title and abstract sifting, 71 treatment-related articles were assessed for eligibility, and nine studies were included at full-text sift.

Seven prospective cohort studies (Table 1) found US-assessed synovitis at baseline could significantly predict treatment response as measured by clinical outcomes such as EULAR response or radiological progression (significance levels ranging from p=0.020 to p=0.04), and power Doppler US could predict treatment tapering or discontinuation failure as measured by relapse or disease flare (p<0.0005 to p=0.06), whereas in most cases clinical measures alone could not. Two RCTs identified suggested US added to DAS-based treatment strategies did not significantly improve primary outcomes (Table 1, ARCTIC p=0.54, TaSER p=0.72 and p=0.33 respectively), but was associated with improved rate of DAS remission (TaSER p=0.03).

Table 1 Characteristics of included studies

Study	Study design	Population and joints	Follow-up	Outcome
Dougados 2013	Prospective cohort	59 RA bDMARD Wrists, MCP, PIP, MTP	2 years	Radiological progression on bDMARD association with baseline US and clinical exam
Ellegaard 2011	Prospective cohort	109 RA starting bDMARD Most affected wrist	1year	Treatment persistence (continued bDMARD) association with baseline US and clinical exam
Inanc 2014	Prospective cohort	43 RA starting bDMARD Joints: 28 according to EULAR guideline	3 months	EULAR response association with baseline US and clinical exam
Iwamoto 2014	Prospective cohort	40 RA, clinical remission, discontinued bDMARDs Joints 40 (134 synovial sites)	6 months	DAS28 relapse and treatment escalation association with baseline US and clinical exam
Luengroongroj 2015	Prospective cohort	32 RA, clinical remission, about to stop or reduce dose DMARD(s), (joints not reported)	3 months	Disease flare following DMARD discontinuation or reduction association with baseline US and clinical exam
Naredo 2014	Prospective cohort	77 RA sustained clinical remission Joints 42 (including hands and feet)	12 months	bDMARD tapering failure association with baseline US and clinical exam
Taylor 2004	Prospective cohort	24 RA Hands and feet	54 weeks	Radiological progression association with baseline US and clinical exam
ARCTIC Haavardsholm 2015	RCT of treatment strategies with and without US	130 RA 44 joints of DAS44	24 months	Composite measure DAS<1.6, SJC44<1, ΔvdHSS<0.5 between 16 and 24 months
TaSER Dale 2016	RCT of treatment strategies with and without US	110 RA 14 joints (PIP, MCP, MTP)	18 months	Mean change from baseline of DAS44, RAMRIS erosion score

bDMARD biological disease modifying anti-rheumatic drug; MCP Metacarpophalangeal; PIP proximal interphalangeal joint; MTP Metatarsalphalangeal; SJC swollen joint count; vdHSS van der Heijde-modified total Sharp Score, RAMRIS rheumatoid arthritis magnetic resonance imaging scoring system.

The search for tapering studies identified nineteen papers.[1] The evidence showed that some patients (proportions varied widely) who had achieved low disease activity could have treatment tapered, with no, or little, short term harm to the patient.

No relevant cost-effectiveness studies were identified and a *de novo* model was constructed. It was considered that evidence from the identified prospective cohort studies and RCTs was not sufficiently robust to populate a model based on current practice. Instead, it was deemed more useful to provide indicative results that focus on the key parameters related to US use, rather than to provide potentially spurious accuracy from a more complex model which could obscure the cost-effectiveness of monitoring synovitis with US. Therefore the modelling undertaken was purposefully simplistic so that the key interactions between monitoring synovitis with US and decisions to influence treatment could be examined explicitly. The parameters used in the base case are shown in Table 2.

Table 2 Model parameters

Parameter	Values	Reference
Cost of an US	£56.66	Assumption based on NHS Resource Costs [39]
Number of US per year per patient	4	Assumption
Annual cost of bDMARD treatment excluding monitoring and administration costs	£9200	Stevenson *et al* [38]
Annual cost of intensive cDMARDs treatment* excluding monitoring and administration costs	£218.17	BNF
Annual cost of oral methotrexate treatment excluding monitoring and administration costs	£39.28	BNF

*Assumed to comprise of methotrexate (20mg weekly), HCQ (6.5mg/kg daily), sulfasalazine (3g daily), and oral prednisolone (7.5mg daily)

For patients where the clinician was contemplating reducing the dose the model estimated the reduction in treatment costs at which point the addition of monitoring synovitis with US became cost-neutral. For patients where the physician was thinking of increasing dosage the reduction in patients escalating treatment at which US was cost-neutral was calculated.

The model estimated (Table 3) that an average reduction of 2.46% in the costs of biological disease-modifying anti-rheumatic drug (bDMARDs) was sufficient to cover the costs of performing US every three months. Assuming a price reduction of 50% (estimated as appropriate if use of biosimilars becomes widespread) then an average reduction of approximately 4.93% in the costs of bDMARDs would render quarterly US monitoring cost neutral.

Table 3 The reduction in drug costs at which using US to monitor synovitis became cost-neutral

	Reduction in total drug costs due to tapering or fewer treatment escalations		Reduction in patients progressing onto	
Parameter	**bDMARD**	**Intensive cDMARDs**	**bDMARD**	**Intensive cDMARDs**
Base case	2.46%	Not possible	2.52%	Not possible
Assuming costs of bDMARDS are 50% of base case (due to biosimilars)	4.93%	Not possible	5.17%	Not possible
Assuming 2 US per year rather than 4	1.23%	51.94%	1.26%	63.34%

CONCLUSIONS

Use of US to monitor synovitis could potentially be a cost-effective approach, given that the proportions of patients for whom clinicians consider amending treatment, would need to taper bDMARD treatment, or not escalation to bDMARDs to negate the costs of US monitoring are low. US could provide clinicians with more confidence in reducing drug burden. However, there is considerable uncertainty in this conclusion due to lack of robust data relating to key parameters.

REFERENCES

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