

evidence | *note*

In response to an enquiry from the Scottish Society for
Rheumatology

Number 70 September 2017

In patients with clinically stable rheumatoid arthritis (clinical remission), can musculoskeletal ultrasound in addition to clinical examination detect or rule out inflammation that predicts subsequent joint damage to inform tapering and discontinuation of therapy?

What is an evidence note?

Evidence notes are rapid reviews of published secondary clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions. Information is available to the topic referrer within a 6-month period and the process of peer review and final publication of the associated advice is usually complete within 6–12 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The draft evidence notes are subject to peer review. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produces an Advice Statement to accompany all evidence reviews.

Key points

- Musculoskeletal ultrasound is an imaging technique that has potential to inform decisions on tapering or discontinuation of therapy in rheumatoid arthritis patients who are in clinical remission.
- Two systematic reviews of observational studies, with overlapping included studies, found that synovitis detected by musculoskeletal ultrasound predicted risk of relapse (including flare) and risk of structural or radiographic progression of disease in rheumatoid arthritis patients in clinical remission.
- A small, low quality randomised controlled trial reported that positive musculoskeletal ultrasound scores were predictors of relapse in rheumatoid arthritis patients in clinical remission who tapered or discontinued treatment.

- Two cohort studies demonstrated that musculoskeletal ultrasound could help identify rheumatoid arthritis patients in clinical remission to inform tapering of biologic therapy and could be used to monitor these patients for relapse.
- A small Scottish evaluation study reported high patient and clinician satisfaction with a pilot musculoskeletal ultrasound clinic within a rheumatology service.

Definitions

Musculoskeletal ultrasound (MSUS): imaging of soft tissues, cartilage, bone surfaces, and fluid containing structures using pulses of high frequency sound^{1, 2}.

Synovitis: inflammation of the synovial tissue lining a joint leading to swelling and pain around the joint³.

Synovial hypertrophy: enlargement or proliferation of cells within the synovial tissue lining a joint, sometimes as a result of inflammation (synovitis)³.

Biologic therapies/biological therapies: newer disease modifying anti-rheumatic drugs which target individual molecules such as the tumour necrosis factor protein⁴.

Literature search

A systematic search of the secondary literature was carried out between 24–30 January 2017 to identify systematic reviews, health technology assessments and other evidence based reports. Medline, Medline ePub ahead of print and in process, Embase, Cinahl and Web of Science databases were also searched for systematic reviews and meta-analyses.

The primary literature was systematically searched between 24–30 January 2017 using the following databases: Medline, Medline ePub ahead of print and in process, Embase, Cinahl and Web of Science.

Key websites were searched for guidelines, policy documents, clinical summaries and economic studies.

All search results were limited to English language from 2007 onwards. Concepts used in all searches included: inflammatory or rheumatoid arthritis, musculoskeletal ultrasound, ultrasonography and tapering. A full list of resources searched and terms used are available on request.

Introduction

Rheumatoid arthritis is a chronic autoimmune condition where an individual's immune system attacks the synovial tissue lining the body's joints causing inflammation, pain, stiffness and joint damage^{5, 6}. Rheumatoid arthritis usually affects both sides of the body in a similar pattern, beginning in the small joints of the hands and feet before spreading to other joints⁶. The exact cause of rheumatoid arthritis is unknown but it appears to involve an environmental trigger initiating a series of changes in the immune system causing it to mistake the body's tissues for foreign tissue which the immune system then attacks. Untreated rheumatoid arthritis can cause irreversible joint damage, restrict an individual's ability to perform everyday tasks such as dressing, cooking or going to work, and reduce quality of life⁷. Life expectancy can be reduced by 3 to 7 years in patients with rheumatoid arthritis who remain untreated and patients with severe disease may live 10 to 15 years less than expected⁷.

Although there is no cure for rheumatoid arthritis, adequate management of the disease allows most people diagnosed with the condition to lead full and active lives⁶. Treatment of rheumatoid arthritis involves using disease modifying anti-rheumatic drugs

(DMARDs), painkillers, anti-inflammatory drugs and steroids to reduce disease activity, preserve physical function and prevent joint damage⁸. Both conventional and biological DMARDs, unlike the other treatments available for rheumatoid arthritis, alter the progression of the disease rather than treating the associated symptoms. As a consequence of advances in treatments for rheumatoid arthritis, clinical remission rates have increased in recent decades. With up to 40% of patients achieving remission status within six months of initiating treatment, disease remission has become a realistic therapeutic goal^{9,10}.

As with many clinical conditions, remission in rheumatoid arthritis has several clinical definitions based on different scoring systems⁹. Remission scoring indices for rheumatoid arthritis include the Disease Activity Score (DAS and DAS-28), the Clinical Disease Activity Index (CDAI) and the Simple Disease Activity Index (SDAI). In addition, the American College of Rheumatology and the European League Against Rheumatism (ACR/EULAR) have produced a set of criteria for defining remission in clinical trials. The different rheumatoid arthritis remission indices are listed in Appendix 1. Although these scoring systems are widely reported in clinical studies, clinicians often make a clinical diagnosis of remission in rheumatoid arthritis patients with joint damage and deformity if ongoing symptoms can be attributed to secondary degenerative disease or fibromyalgia (Dr Stephen Kelly, Consultant Rheumatologist, Barts Health NHS Trust. Personal communication, 25 May 2017). In clinical practice in Scotland, the most commonly used scoring system is the DAS-28 which is used in conjunction with clinical judgement (Dr Neil McKay, Consultant Rheumatologist, NHS Lothian. Personal communication, 26 June 2017).

With remission rates increasing and concerns over the safety and cost of long term treatment of rheumatoid arthritis, particularly with biologic therapies, there is growing interest in tapering or stopping treatment in rheumatoid arthritis patients achieving clinical remission^{10,11}. Musculoskeletal ultrasound could inform

decisions on tapering or discontinuation of therapy in patients with rheumatoid arthritis who are in clinical remission.

Health technology description

Musculoskeletal ultrasound is a rapid, non-radioactive method of imaging soft tissues, cartilage, bone surfaces and fluid containing structures using high frequency sound^{1,2}. In patients with rheumatoid arthritis, ultrasound imaging is used to detect pathological features of the disease such as synovitis¹².

In the past decade there have been improvements in image definition, size, portability and cost of ultrasound machines². Most ultrasound machines now have built-in settings for musculoskeletal imaging². Each ultrasound machine comprises a computer processing unit and a transducer¹. The transducer produces pulses of high frequency sound, inaudible to the human ear, that reflect back from the body tissues as echoes which are picked up by the transducer and passed to the computer processing unit¹. The computer processing unit interprets the echoes to produce images of the body tissues¹.

There are two main musculoskeletal ultrasound modalities: grey-scale/B-mode ultrasound and power Doppler ultrasound¹². Grey-scale ultrasound produces anatomical structural images in black, white and shades of grey allowing the visualisation of synovial hypertrophy, synovitis and/or effusion^{2,12}. The more dense a body tissue is, the more it reflects sound back to the transducer and the whiter it appears in the image^{1,2}. Power Doppler ultrasound uses the principle that sound echoes differently from objects that are moving towards or away from the transducer (the 'Doppler effect') to visualise blood flow in tissues^{1,2,12}. In rheumatoid arthritis with active synovitis, blood flow through small blood vessels in the synovial tissues surrounding the affected joints increases and can be detected by Doppler ultrasound. Power Doppler ultrasound images appear as colour superimposed onto the grey-scale ultrasound image².

Image resolution and depth of tissue penetration with ultrasound varies depending on the frequency of sound used. Low frequency sound penetrates to greater depths but produces poorer image resolution¹. Musculoskeletal ultrasound imaging uses sound frequencies of 7MHz and above to provide sufficient tissue penetration and image resolution¹. Many other factors influence the quality of the image obtained using musculoskeletal ultrasound such as the type of machine, transducer settings, transducer pressure and patient position². For musculoskeletal ultrasound, a linear array which has a flat surface and produces rectangular images is preferred^{1, 2}.

The potential benefits of using ultrasound in rheumatoid arthritis patients include the ability to carry out imaging in rheumatology clinics or at the patient bedside, low running costs and less image corruption by metal artifacts than CT or MRI imaging². Counter-balancing these benefits are initial equipment costs, the resource impact of training staff to use ultrasound and dependency on operator skills and experience^{1, 2}.

Epidemiology

Rheumatoid arthritis can develop at any age with peak incidence in people aged 40 to 60 years old⁶.

In the UK, the main source of epidemiological data on rheumatoid arthritis is the Arthritis UK funded Norfolk Arthritis Register (NOAR). Based on NOAR data, incidence rates for rheumatoid arthritis appear to be stable with an estimated 1,851 new cases in Scotland in 2009¹³. An estimated 36,835 people in Scotland were living with rheumatoid arthritis in 2009; approximately 73% of these patients were women¹³. However, incidence and prevalence estimates for rheumatoid arthritis in Scotland derived from NOAR data should be interpreted with caution due to geographical variation in clinical practice¹³.

More recent prevalence estimates from the 2014 Quality and Outcomes Framework

indicator on rheumatoid arthritis put prevalence in Scotland at 0.6% (approximately 32,085 people in 2014)¹⁴. With an increasing older population in Scotland, the prevalence of rheumatoid arthritis is expected to increase in future¹³.

Clinical effectiveness

Two systematic reviews with complete overlap of included studies were identified. One of these systematic reviews included a meta-analysis. Three primary studies published after the review inclusion periods were also included in this review.

Outcomes reported in the published literature on musculoskeletal ultrasound in rheumatoid arthritis patients in remission are relapse, flare and progression of joint damage^{8, 10, 11, 15, 16}. No consistently applied definition of these outcomes was found in the literature. Relapse is generally described as a rising DAS score indicating an increase in disease activity and resulting in the loss of remission or low disease status (Dr Neil McKay, Consultant Rheumatologist, NHS Lothian. Personal communication, 11 Apr 2017). Flares are a largely patient defined outcome that is not clearly described in the studies included in this review. A specialist interest group has described a flare as any worsening of disease activity, represented by a cluster of symptoms, which would result in a treatment change if it persisted¹⁷. From this definition and the published literature, a flare appears to be a resurgence in symptoms (often patient reported) that may or may not require an increase in treatment and could indicate a relapse. Progression is defined as further structural damage to affected joints that may be visible on imaging. All of the studies identified used detection of synovitis or synovial hypertrophy on ultrasound images as indicators of relapse, flare or progression of joint damage.

In a well-reported systematic review with meta-analysis of observational studies, synovitis detected on musculoskeletal ultrasound was predictive of future relapse or structural progression of disease in patients with

rheumatoid arthritis in clinical remission¹⁵. All the included studies were of moderate to good quality based on criteria defined by the review authors (study participation, attrition, measurement of prognostic factors, controlling for confounding, measurement of outcomes and approach to analysis). The systematic review incorporated a total of 19 studies with 1,618 participants, although not all of these studies contributed to the meta-analyses. The majority of study participants included in the meta-analyses were classed as being in clinical remission (557 participants) based on DAS, DAS-28, SDAI or the ACR/EULAR criteria. The three small separate meta-analyses reported in the review appear to incorporate only patients in remission but this is not specifically stated. Five studies using combined grey-scale and power Doppler ultrasound were incorporated into the first meta-analysis, which assessed long term risk of relapse. After excluding one study with a shorter follow-up period and participants at an earlier stage of rheumatoid arthritis to reduce heterogeneity, there was a significant association between ultrasound detected synovitis and the odds of relapse in patients with rheumatoid arthritis in clinical remission (odds ratio (OR) 3.2, 95% confidence interval (CI) 1.8 to 5.9, 4 studies, n=266, p<0.001, I²=0%). Relapse was defined as increasing disease activity or flares requiring a change in therapy. In a second patient level meta-analysis, ultrasound detected synovitis was associated with increased odds of structural progression of joint damage (OR 9.13, 95% CI 1.1 to 74.3, 3 studies, n=173, p=0.04, I²=43%). In this analysis the results were borderline for statistical significance and the confidence interval was very wide, indicating a lack of certainty around the odds ratio estimate. Structural progression was not defined by the review authors and there was moderate heterogeneity in this meta-analysis that could not be explained. A final joint level meta-analysis reported that ultrasound detected synovitis was associated with increased odds of structural progression of joint damage in rheumatoid arthritis patients in clinical remission (OR 6.95, 95% CI 3.4 to 13.9, 2 studies, 798 joints, p<0.0001, I²=6%). The results of this joint level

analysis are largely driven by one study which was heavily weighted (88%).

An older systematic review (2013)¹⁶ incorporated five of the studies used in the meta-analyses by Nguyen et al (2014)¹⁵. In this older systematic review, outcomes are described as flare and radiographic progression¹⁶. Neither of these outcomes are specifically defined in the systematic review but they appear to be analogous to relapse and structural progression as reported in the meta-analysis by Nguyen et al (2014)¹⁵. The two systematic reviews, therefore, include the same studies and report the same outcomes, although they are described differently, and reach similar conclusions. However, the older systematic review by Ten Cate et al (2013)¹⁶ does not conduct any meta-analyses due to high heterogeneity, while Nguyen et al (2014)¹⁵ reported meta-analyses based on these same studies. Therefore, the results of the systematic review by Ten Cate et al (2013)¹⁶ are presented below for comparison, but should not be interpreted as providing additional studies to the meta-analysis by Nguyen et al (2014)¹⁵.

Ten Cate et al (2013) assessed the quality of included studies using author defined criteria. The studies all appear to have some limitations based on these criteria. Four studies assessed the predictive ability of musculoskeletal ultrasound for flares in rheumatoid arthritis patients in remission¹⁶. Two studies reported that signs of synovitis on power Doppler ultrasound predicted the occurrence of flares (OR 3.6, 95% CI 1.4 to 9.0, n=94, and OR 13, 95% CI 1.6 to 104, n=43); one reported that synovitis on power Doppler ultrasound predicted the occurrence of flares within one year (OR 6.3, 95% CI 2.0 to 20, n=85), and one study did not find ultrasound useful for predicting flares. There are substantial differences in the odds ratios in these studies compared to each other and to the odds ratios reported in the equivalent meta-analysis in Nguyen et al (2014)^{15, 16}. It is possible these differences are the result of heterogeneity between studies due to variation in patient characteristics, definitions of remission, or definitions of the outcomes

reported. Two further studies in the review by Ten Cate et al (2013) evaluated the utility of ultrasound for detecting radiographic progression of joint damage. The first study, which analysed results at the patient level, reported that synovitis detected on power Doppler ultrasound increased the risk of radiographic progression of joint damage (OR 1.4, 95% CI 1.1 to 1.9, n=85), but synovitis detected on grey-scale ultrasound alone did not predict radiographic progression of joint damage (OR 1.92, 95% CI 0.49 to 7.24). A second study, which analysed results at the joint level, found that signs of inflammation on power Doppler ultrasound predicted radiographic progression of joint damage in patients with rheumatoid arthritis in clinical remission (OR 12, 95% CI 3.3 to 44, n=102). Reported confidence intervals were broad in all studies in the review, particularly for the occurrence of flares, indicating a lack of precision in the estimates.

Three primary studies were published after the date of the literature searches in the systematic reviews described above^{8, 10, 11}. These three studies assess whether musculoskeletal ultrasound can help identify rheumatoid arthritis patients in clinical remission who could taper or discontinue their medication, and whether ultrasound can aid in monitoring these patients for relapse following tapering or discontinuation of therapy.

A randomised controlled trial (RCT) assessed how many rheumatoid arthritis patients sustained remission for 12 months after tapering or discontinuing therapy. A secondary outcome was whether clinical assessment, laboratory measures or ultrasound could predict relapse in patients who tapered or discontinued treatment¹⁰. Rheumatoid arthritis patients in sustained clinical remission for 6 months or more were allocated to five treatment arms that continued, tapered (50% reduction) or stopped DMARDs and/or biologic therapies. It is unclear why all combinations of continuation, tapering and stopping of therapies were not included. For example, there is no study group where full dose DMARD therapy is continued and biologic therapy is stopped. No details are provided on

participant randomisation or allocation concealment which may have introduced bias to the study. Only patients who volunteered to discontinue treatment were enrolled which may introduce further bias. Patients were evaluated monthly by clinical assessment, blood tests and ultrasound during the 12-month follow-up period. Ultrasonographers were blinded to patient disease activity scores and laboratory test results. Of the 157 participants enrolled in the trial, 49.7% (n=78) remained in remission after one year¹⁰. In a Cox logistic regression analysis both grey-scale and power Doppler ultrasound scores were predictors of the odds of relapse in rheumatoid arthritis patients after 3 months of tapering or discontinuing treatment. The probability of relapse was 1.59 times greater for every one unit increase in grey-scale ultrasound score (OR 1.59, 95% CI 1.15 to 2.22, p=0.006) and 2.12 times greater with every one unit increase in power Doppler ultrasound score (OR 2.12, 95% CI 1.04 to 4.31, p=0.039). The results of the study are not clearly presented by treatment group and participant characteristics are lacking which limits generalisability of the results. All patients who relapsed were returned to their baseline treatment level and achieved clinical remission again within 4 months.

A cohort study measured whether ultrasound could be used to select rheumatoid arthritis patients in clinical remission who could taper and discontinue biologic therapy¹¹. This small prospective study enrolled 42 consecutive rheumatoid arthritis patients with a DAS score less than 1.6 at three consecutive evaluations 3 months apart. Patients did not self-select for dose reduction; all patients in stable clinical remission tapered and, if still clinically stable, discontinued biologic therapy. This should reduce the risk of bias in the study. A single ultrasonographer, blinded to clinical assessment and laboratory test results, scanned each patient using combined grey-scale and power Doppler ultrasound at baseline, initiation of treatment tapering, discontinuation of therapy, and every 3 months after that. After 3 months of tapering biologic therapies, 30.9% (n=13) of participants relapsed. Relapse was defined as a change in DAS score >1.2 from the value at baseline

ultrasound assessment. Patients who relapsed after tapering biologic therapy had significantly higher ultrasound detected levels of synovial hypertrophy at the fifth metatarsophalangeal (MTP) joint on the day of first tapering compared to patients who did not relapse after 3 months ($p=0.01$). Greater synovial hypertrophy was detected at the fifth MTP joint in an additional three patients who relapsed during the 6 months where biologic therapy was discontinued ($p=0.04$).

In a UK-based cohort study, combined clinical and ultrasound assessment of remission in routine care of rheumatoid arthritis patients helped identify patients who could reduce their dose of biologic therapy⁸. Patients with rheumatoid arthritis receiving biologic therapy selected from a wider rheumatology department patient list were enrolled in the study. It is unclear if this selection process could have introduced bias into the study by selecting a subset of rheumatoid arthritis patients. Forty percent of patients eligible to reduce their biologic therapy agreed to participate in the study and reduce their dose by one third ($n=70$). This participant self-selection may have biased the results as a higher proportion of older patients agreed to reduce their treatment dose (mean \pm SD age 61.86 ± 12.81 years versus 57.74 ± 14.06 years, $p=0.039$). The study authors speculated this may be due to greater concerns among younger patients that loss of remission could affect their ability to work. During 18 months of follow-up, the proportion of patients who tapered therapy and maintained remission decreased from 96% ($n=67$) at 3 months to 34% ($n=24$) at 18 months. Clinical remission was defined as a DAS-28 score less than 2.6 and ultrasound remission was defined as no evidence of synovitis on power Doppler ultrasound of the hand and wrist. Of the patients who experienced a flare or relapse, 50% demonstrated development of further synovitis either on ultrasound only or on both ultrasound and remission scores. This suggests that ultrasound contributes additional information to clinical examination for detecting relapse in rheumatoid arthritis patients in remission who taper biologic therapy. Patient reported flares

occurred in three participants despite remaining in clinical and ultrasound defined remission. Patients who experienced a flare or relapse were re-escalated to the full treatment dose received at baseline. After an average of 15 months follow-up, five patients out of 32 who relapsed were still experiencing moderate disease activity despite re-escalation of biologic therapy.

Patient and clinician experiences

In 2012, the National Rheumatoid Arthritis Society (UK) conducted a survey of rheumatoid arthritis patients to explore experiences of living with rheumatoid arthritis and patient understanding of the term 'remission'¹⁸. Over a period of 2 months, 1,100 rheumatoid arthritis patients responded to the survey. One of the key findings in the survey report was that: *"There is a mismatch between how HCPs [health care providers] define remission and what people with RA [rheumatoid arthritis] understand by the term"*¹⁸. Only 13% of respondents associated the DAS-28 score with remission and 64% did not know how healthcare providers defined remission. Fifty-five percent of respondents did not know if reaching clinically-defined remission was a realistic treatment goal. From a patient's perspective, remission meant being symptom free (50%) or pain free (48%). Approximately a quarter of respondents described remission as being able to perform tasks such as exercising, walking and taking up a hobby.

A small, non-comparative observational study evaluated clinical usefulness of, and patient satisfaction with, a pilot musculoskeletal ultrasound clinic in Inverness, Scotland¹⁹. Over a 6-month period, 10 evening ultrasound clinics were organised. Clinicians were encouraged to refer patients with suspected or diagnosed inflammatory arthritis to the ultrasound clinic based on four pre-specified indications: assisting with early or subclinical diagnosis, aiding treatment decision-making, monitoring disease activity or response to treatment, and performing ultrasound guided procedures. Forty-three clinicians (rheumatologists, rheumatology nurses, physiotherapists) and 43 patients were sent a questionnaire following

patient attendance at one of the ultrasound clinics. Survey response rates were 96% for clinicians (n=39) and 44.2% for patients (n=19).

Patients expressed high satisfaction with the ultrasound clinic¹⁹. On a Likert scale of 0 to 10, average patient satisfaction scores were 9.5 or higher for explanations of the procedure and findings, lack of discomfort during the procedure, improved understanding of their condition, length of appointment and willingness to return for future ultrasounds. Clinicians reported that ultrasound results were used to monitor disease activity or treatment response in 39% of patients referred to the pilot clinic (n=17)¹⁹. This referral category (monitoring disease activity or treatment response) could have included supporting decisions to de-escalate treatment in patients in clinical remission. Thirty-five percent (n=15) of clinicians used the ultrasound results to aid early or sub-clinical diagnosis and 44% (n=19) of clinicians used the ultrasound results to aid treatment decision-making. Average clinician scores on usefulness of ultrasound for the referral indications ranged from 8.0 to 8.7 on a 10-point Likert scale. The clinicians scored the musculoskeletal ultrasound clinic an average 9.0 out of 10 for providing valuable support to the rheumatology team.

Safety

No adverse events relating to the use of musculoskeletal ultrasound in patients with rheumatoid arthritis in clinical remission were identified.

Cost effectiveness

No cost-effectiveness evidence was identified relating to musculoskeletal ultrasound in people with rheumatoid arthritis in clinical remission.

Conclusion

A systematic review and a meta-analysis based on a total of seven small studies suggest that

synovitis or inflammation detected on musculoskeletal ultrasound is predictive of relapse or progression of joint damage in rheumatoid arthritis patients in clinical remission. Evidence from three additional primary studies suggests that musculoskeletal ultrasound is effective for identifying rheumatoid arthritis patients in clinical remission who are suitable for tapering or discontinuation of therapy and monitoring these patients for relapse or flares.

In a UK survey of rheumatoid arthritis patients, patient understanding of remission differed notably from clinical definitions of remission. A small Scottish evaluation study reported high patient and clinician satisfaction with a pilot musculoskeletal ultrasound clinic within a rheumatology service.

No adverse events relating to the use of musculoskeletal ultrasound in patients with rheumatoid arthritis in clinical remission were identified.

No evidence was identified which assessed cost effectiveness of musculoskeletal ultrasound in people with rheumatoid arthritis in clinical remission. Therefore, no conclusions can be drawn about the cost effectiveness of musculoskeletal ultrasound in this population.

Identified research gaps

Cost-effectiveness analyses with a UK perspective are required to evaluate use of musculoskeletal ultrasound to inform tapering and discontinuation of therapy in patients with rheumatoid arthritis in clinical remission, with particular focus on quality of life and patient-reported outcomes.

Primary observational studies are required to establish the optimal set of joints for assessment with ultrasound imaging that identifies patients in clinical and imaging remission. Such studies should also consider the frequency of ultrasound monitoring of patients in clinical remission

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

About evidence notes

This evidence note will be considered for review 2 years post-publication, and at 2-yearly intervals thereafter. For further information about the evidence note process see:

www.healthcareimprovementscotland.org/our_work/clinical_cost_effectiveness/shtg/standard_operating_procedures.aspx

To propose a topic for an evidence note, email shtg.hcis@nhs.net

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

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References

1. Chaturvedi V. Musculo-skeletal ultrasound in rheumatology practice. *J Assoc Physicians India*. 2014;62:36-40.
2. Arthritis Research UK. Topical reviews: ultrasound in rheumatology. 2011 [cited 17 Mar 2017]; Available from: <http://www.arthritisresearchuk.org/health-professionals-and-students/reports/topical-reviews/topical-reviews-summer-2011.aspx>.
3. Dorland WAN. *Dorland's illustrated medical dictionary*. 29th ed. Philadelphia: WB Saunders Company; 2000.
4. Arthritis Research UK. Disease modifying anti-rheumatic drugs (DMARDs). c2017 [cited 2017 Sept 07]; Available from: <https://www.arthritisresearchuk.org/arthritis-information/drugs/dmards.aspx>.
5. Arthritis Research UK. What is rheumatoid arthritis? c2016 [cited 28 Feb 2017]; Available from: <http://www.arthritisresearchuk.org/arthritis-information/conditions/rheumatoid-arthritis/what-is-rheumatoid-arthritis.aspx>.
6. National Rheumatoid Arthritis Society. What is rheumatoid arthritis? 2014 [cited 28 Feb 2017]; Available from: http://www.nras.org.uk/what-is-ra-article#What%20is_RA?
7. British Society for Rheumatology. Simple tasks: fast facts. 2013 [cited 28 Feb 2017]; Available from: http://www.rheumatology.org.uk/includes/documents/cm_docs/2013/s/simple_tasks_fast_facts_pdf.pdf.
8. Marks JL, Holroyd CR, Dimitrov BD, Armstrong RD, Calogeras A, Cooper C, *et al*. Does combined clinical and ultrasound assessment allow selection of individuals with rheumatoid arthritis for sustained reduction of anti-tumor necrosis factor therapy? *Arthritis Care Res (Hoboken)*. 2015;67(6):746-53.
9. Ben Abdelghani K, Miladi S, Souabni L, Kassab S, Chekili S, Laatar A, *et al*. Role of ultrasound in assessing remission in rheumatoid arthritis. *Diagnostic and interventional imaging*. 2015;96(1):3-10. Epub 2014/09/16.
10. El Miedany Y, El Gaafary M, Youssef S, Ahmed I, Bahlas S, Hegazi M, *et al*. Optimizing therapy in inflammatory arthritis: prediction of relapse after tapering or stopping treatment for rheumatoid arthritis patients achieving clinical and radiological remission. *Clin Rheumatol*. 2016;35(12):2915-23.
11. Alivernini S, Peluso G, Fedele AL, Tolusso B, Gremese E, Ferraccioli G. Tapering and discontinuation of TNF-alpha blockers without disease relapse using ultrasonography as a tool to identify patients with rheumatoid arthritis in clinical and histological remission. *Arthritis Res Ther*. 2016;18:39.
12. Bhasin S, Cheung PP. The role of power Doppler ultrasonography as disease activity marker in rheumatoid arthritis. *Disease Markers*. 2015:325909.
13. Scottish Public Health Network. Health care needs assessment of services for adults with rheumatoid arthritis. Part B: epidemiology of RA in Scotland. 2012 [cited 15 Mar 2017]; Available from: http://www.scotphn.net/wp-content/uploads/2016/03/2012_09_12-PART-B_RA-HCNA_EPIDEMIOLOGY-ES-V2-1.pdf.
14. ISD Scotland. Quality and outcomes framework: rheumatoid arthritis. c2016 [cited 28 Feb 2017]; Available from: <http://www.isdscotland.org/Health-Topics/General-Practice/Quality-And-Outcomes-Framework/Information-for-users-of-QOF-register-and-prevalence-data.asp>.
15. Nguyen H, Ruysen-Whitrand A, Gandjbakch F, Constantin A, Foltz V, Cantagrel A. Prevalence of ultrasound-detected residual synovitis and risk of relapse and structural progression in rheumatoid arthritis patients in clinical remission: a systematic review and meta-analysis. *Rheumatology (Oxford)*. 2014;53(11):2110-8.
16. Ten Cate DF, Luime JJ, Swen N, Gerards AH, De Jager MH, Basoski NM, *et al*. Role of ultrasonography in diagnosing early rheumatoid arthritis and remission of rheumatoid arthritis--a systematic review of the literature. *Arthritis Res Ther*. 2013;15(1):R4.
17. Bingham CO, Pohl C, Woodworth TG, Hewlett SE, May JE, Rahman MU, *et al*. Developing a standardized definition for disease "flare" in rheumatoid arthritis (OMERACT 9 special interest group). *J Rheumatol*. 2009;36:2335-41.

18. National Rheumatoid Arthritis Society. What does remission mean to you? Understanding and improving communications between people with rheumatoid arthritis and their healthcare professionals. 2014 [cited; Available from: http://www.nras.org.uk/data/files/About%20RA/How%20is%20RA%20managed/what_does_remission_mean_to_you_report.pdf].
19. Acebes C, Harvie JP, Wilson A, Duthie J, Bowen F, Steven M. Clinical usefulness and patient satisfaction with a musculoskeletal ultrasound clinic: results of a 6-month pilot service in a Rheumatology Unit. *Rheumatol Int.* 2016;36(12):1677-81.