Specialist Pharmacy Service

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A summary of prescribing recommendations from NICE guidance

Rheumatoid arthritis in adults: management

NICE NG100; 2018

This guideline covers the diagnosis and management of rheumatoid arthritis in adults.

Definition of terms

anti-CCP	anti-cyclic citrullinated peptide
cDMARDS	conventional disease-modifying anti-rheumatic drugs
CI	contraindicated
DAS28	composite Disease Activity Score
EULAR	European League Against Rheumatism
HAQ	Health Assessment Questionnaire
MDT	multidisciplinary team
NSAIDs	non-steroidal anti-inflammatory drugs
PAS	patient access scheme
PPI	proton pump inhibitor
RA	rheumatoid arthritis
TENS	transcutaneous electrical nerve stimulation

Diagnosis

When to refer for specialist opinion

- Refer any adult with suspected persistent synovitis of undetermined cause.
- Refer urgently (even with a normal acute-phase response, negative anti-CCP antibodies or rheumatoid factor) if any of the following apply:
  - the small joints of the hands or feet are affected,
  - more than one joint is affected,
  - there has been a delay of ≥3 months between onset of symptoms and seeking medical advice.

Investigations

- If the following investigations are ordered in primary care, they should not delay referral for specialist opinion (see above).
- Offer to carry out a blood test for rheumatoid factor in adults with suspected RA who are found to have synovitis on clinical examination.
- Consider measuring anti-CCP antibodies in adults with suspected RA if they are negative for rheumatoid factor.
- X-ray the hands and feet in adults with suspected RA and persistent synovitis.

Investigations following diagnosis

- As soon as possible after establishing a diagnosis of RA:
  - measure anti-CCP antibodies, unless already measured to inform diagnosis,
  - X-ray the hands and feet to establish whether erosions are present, unless X-rays were performed to inform diagnosis,
  - measure functional ability e.g. using HAQ, to provide a baseline for assessing the functional response to treatment.
- If anti-CCP antibodies are present or there are erosions on X-ray:
  - advise the person that they have an increased risk of radiological progression but not necessarily an increased risk of poor function, **AND**
  - emphasise the importance of monitoring their condition, and seeking rapid access to specialist care if disease worsens or they have a flare.

Information and support

- Explain risks and benefits of treatment options to adults with RA in ways that can be easily understood. Throughout the course of their disease, offer the opportunity to talk about and agree all aspects of their care, and respect the decisions they make.
- Offer verbal and written information to:
  - improve their understanding of the condition and its management, **AND**
  - counter any misconceptions they may have.
- Adults with RA who wish to know more about their disease and its management should be offered the opportunity to take part in existing educational activities, including self-management programmes.

Treatment and management

MDT

- Adults with RA should have:
  - ongoing access to a MDT. This should provide opportunity for periodic assessments of the effect of the disease on their lives (such as pain, fatigue, everyday activities, mobility, ability to work or take part in social or leisure activities, quality of life, mood, impact on sexual relationships) and help to manage the condition,h
  - access to a named member of the MDT (e.g. specialist nurse) who is responsible for coordinating their care.

Pharmacological treatment

Treat-to-target strategy

- Treat active RA in adults with the aim of achieving a target of remission or low disease activity if remission cannot be achieved (treat-to-target).
- Consider making the target remission rather than low disease activity for people with an increased risk of radiological progression (presence of anti-CCP antibodies or erosions on X-ray at baseline assessment).
- In adults with active RA, measure C-reactive protein and disease activity (using a composite score such as DAS28) monthly in specialist care until the target of remission or low disease activity is achieved.

Monotherapy

For adults with newly diagnosed active RA:

- ***First-line***: offer treatment with cDMARD monotherapy using oral methotrexate, leflunomide or sulfasalazine as soon as possible and ideally within 3 months of onset of persistent symptoms.
- Consider hydroxychloroquine for first-line treatment as an alternative to oral methotrexate, leflunomide or sulfasalazine for mild or palindromic disease.
- Escalate dose as tolerated.
- Consider short-term bridging treatment with glucocorticoids (oral, intramuscular or intra-articular) when starting a new cDMARD.

Please go to www.nice.org.uk to check for any recent updates to this guideline.

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RA in adults: ……continued

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Step-up treatment

- Offer additional cDMARDs (oral methotrexate, leflunomide, sulfasalazine or hydroxychloroquine) in combination in a step-up strategy when treatment target has not been achieved despite dose escalation.

Further pharmacological treatment – see Biological and other immunomodulatory therapies (page 3-4)

Symptom control

- Consider oral NSAIDs (including traditional NSAIDs and cox II selective inhibitors) when control of pain or stiffness is inadequate. Take account of potential gastrointestinal, liver and cardio-renal toxicity, and the person's risk factors, including age and pregnancy.
- When treating symptoms of RA with oral NSAIDs:
  - offer the lowest effective dose for the shortest possible time, **AND**
  - offer a PPI, **AND**
  - review risk factors for adverse events regularly.
- If a person with RA needs to take low-dose aspirin, healthcare professionals should consider other treatments before adding an NSAID (with a PPI) if pain relief is ineffective or insufficient.

Managing flares

- Offer short-term treatment with glucocorticoids for managing flares in adults with recent-onset or established disease to rapidly decrease inflammation.
- In adults with established RA, only continue long-term treatment with glucocorticoids when:
  - the long-term complications of glucocorticoid therapy have been fully discussed, **AND**
  - all other treatment options (including biological and other immunomodulatory therapies) have been offered.

Non-pharmacological management

Physiotherapy

- Adults with RA should have access to specialist physiotherapy, with periodic review, to:
  - improve general fitness and encourage regular exercise,
  - learn exercises for enhancing joint flexibility, muscle strength and managing other functional impairments,
  - learn about short-term pain relief provided by methods such as TENS and wax baths.

Occupational therapy

- Adults with RA should have access to specialist occupational therapy, with periodic review, if they have:
  - difficulties with any of their everyday activities, **OR**
  - problems with hand function.

Hand exercise programmes

- Consider a tailored strengthening and stretching hand exercise programme for adults with RA with pain and dysfunction of the hands or wrists if:
  - they are not on a drug regimen for RA, **OR**
  - they have been on a stable drug regimen for at least 3 months.
- The tailored hand exercise programme for adults with RA should be delivered by a practitioner with training and skills in this area.

Podiatry

- All adults with RA and foot problems should have access to a podiatrist for assessment and periodic review of their foot health needs.
- Functional insoles and therapeutic footwear should be available if indicated.

Diet and complementary therapies

- Inform adults with RA who wish to experiment with their diet that there is no strong evidence that their arthritis will benefit. However, they could be encouraged to follow the principles of a Mediterranean diet (more bread, fruit, vegetables and fish; less meat; and replace butter and cheese with products based on vegetable and plant oils).
- Inform adults with RA who wish to try complementary therapies that although some may provide short-term symptomatic benefit, there is little or no evidence for their long-term efficacy.
- If an adult with RA decides to try complementary therapies, advise them:
  - these approaches should not replace conventional treatment,
  - this should not prejudice the attitudes of members of the MDT, or affect the care offered.

Psychological interventions

- Offer psychological interventions (e.g. relaxation, stress management and cognitive coping skills, such as managing negative thinking) to help adults with RA adjust to living with their condition.
- See **NICE CG91; 2009: Depression in adults with a chronic physical health problem.**

Monitoring

- Ensure that all adults with RA have:
  - rapid access to specialist care for flares, **AND**
  - information about when and how to access specialist care, **AND**
  - ongoing drug monitoring.
- Consider a review appointment to take place 6 months after achieving treatment target to ensure that the target has been maintained.
- Offer all adults with RA, including those who have achieved the treatment target, an annual review to:
  - assess disease activity and damage, and measure functional ability (e.g. using HAQ),
  - check for development of comorbidities, such as hypertension, ischaemic heart disease, osteoporosis and depression,
  - assess symptoms that suggest complications, such as vasculitis and disease of the cervical spine, lung or eyes,
  - organise appropriate cross referral within the MDT,
  - assess the need for referral for surgery (see **Surgical treatment**),
  - assess the effect the disease is having on a person's life.
- For adults who have maintained treatment target for at least 1 year without glucocorticoids, consider cautiously reducing drug doses or stopping drugs in a step-down strategy. Return promptly to the previous DMARD regimen if the treatment target is no longer met.
- **Do NOT** use ultrasound for routine monitoring of disease activity in adults with RA.

Recommendations – wording used such as 'offer' and 'consider' denote the strength of the recommendation.

Drug recommendations – the guideline assumes that prescribers will use a drug's Summary of Product Characteristics (SPC) to inform treatment decisions.

RA in adults: ……continued
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Surgical treatment
- Offer to refer adults with RA for an early specialist surgical opinion if any of the following do not respond to optimal non-surgical management:
  - persistent pain due to joint damage or other identifiable soft tissue cause,
  - worsening joint function ,
  - progressive deformity,
  - persistent localised synovitis.
- Offer to refer adults with any of the following complications for a specialist surgical opinion before damage or deformity becomes irreversible:
  - imminent or actual tendon rupture,
  - nerve compression (e.g. carpal tunnel syndrome),
  - stress fracture.
- When surgery is offered explain that the main expected benefits are:
  - pain relief,
  - improvement, or prevention of further deterioration, of joint function,
  - prevention of deformity.
- Cosmetic improvements should not be the dominant concern.
- Offer urgent combined medical and surgical management to adults with RA who have suspected or proven septic arthritis (especially in a prosthetic joint).
- If an adult with RA develops any symptoms or signs that suggest cervical myelopathy (e.g. paraesthesia, weakness, unsteadiness, reduced power, extensor plantars):
  - request an urgent MRI scan, **AND**
  - refer for a specialist surgical opinion.
- Do not let concerns about long-term durability of prosthetic joints influence decisions to offer joint replacements to younger adults with RA.

Interventional procedures – see NICE Pathway

Total hip replacement and resurfacing arthroplasty for end stage arthritis of the hip – see NICE Pathway

NICE Technology Appraisals; Biological and other immunomodulatory therapies for RA

See **NICE Pathway; Rheumatoid arthritis**

Prescribing
General principles
- Start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may need to be varied for some people because of differences in the mode of administration and treatment schedules.
- Continue treatment only if there is adequate/moderate response at 6 months after initiation of treatment (assessed using either DAS28/EULAR*). After an initial response within 6 months withdraw treatment if response is not maintained.
- People whose treatment is not recommended in NICE guidance, but was started within the NHS before guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

Biological and other immunomodulatory therapies

Inadequate response to cDMARDs
Biologicals
NICE TA375; 2016 Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for RA not previously treated with DMARDs or after cDMARDs only have failed

NICE TA485; 2017 Sarilumab for moderate to severe RA

- **Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept**, and **sarilumab** are recommended as treatment options in **combination with methotrexate** only if:
  - disease is severe, **AND**
  - disease has not responded to intensive therapy with a combination of cDMARDs, **AND**
  - the companies provide certolizumab pegol, golimumab, abatacept, tocilizumab and sarilumab, as agreed in the PAS.

* Check individual **NICE TA** documents for recommendations on appropriate monitoring for specific therapies.

- **Adalimumab, etanercept, certolizumab pegol, tocilizumab, and sarilumab**, can be used as **monotherapy** for people who cannot take methotrexate because it is CI or because of intolerance, when the criteria above are met.

Anakinra
- On the balance of its clinical benefits and cost effectiveness, anakinra is **NOT** recommended for the treatment of RA, except in the context of a controlled, long-term clinical study.
- Patients currently receiving anakinra may suffer loss of wellbeing if their treatment were discontinued at a time they did not anticipate. Therefore, patients should continue therapy until they and their consultant consider it is appropriate to stop.
- **Do NOT** offer the combination of TNF-α inhibitor therapy and anakinra for RA.

See **NICE MIB126 Medtech innovation briefing; Promonitor for monitoring response to biologics in rheumatoid arthritis**

Other immunomodulatory therapies
Tofacitinib and baricitinib
NICE TA480; 2017 Tofacitinib for moderate to severe RA
NICE TA466; 2017 Baricitinib for moderate to severe RA

- **Tofacitinib** and **baricitinib** are recommended as options in **combination with methotrexate** only if:
  - disease is severe, that is, a DAS28 >5.1, **AND**
  - disease has not responded to intensive therapy with a combination of cDMARDs, **AND**
  - the companies provide tofacitinib and baricitinib as agreed in the PAS.
- **Tofacitinib** and **baricitinib** can be used as monotherapy for people who cannot take methotrexate because it is CI or because of intolerance, when the criteria above are met.

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RA in adults: ……continued
NG100:2018 and NICE TAs

Inadequate response or intolerance to biological DMARDs and rituximab is suitable
NICE TA195; 2010 Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of RA after the failure of a TNF inhibitor

- Rituximab in **combination with methotrexate** is recommended as an option for the treatment of adults with severe active RA who have had an inadequate response to, or are intolerant of, other DMARDs, including at least one TNF inhibitor. Treatment with rituximab should be given no more frequently than every 6 months.
- Treatment with rituximab in combination with methotrexate should be continued only if there is an adequate response following initiation of therapy and an adequate response is maintained following retreatment with a dosing interval of at least 6 months. An adequate response is defined as an improvement in DAS28 of ≥1.2 points.
- When using DAS28, healthcare professionals should take into account any physical, sensory or learning disabilities, communication difficulties, or disease characteristics that could adversely affect patient assessment and make any adjustments they consider appropriate.
- A team experienced in the diagnosis and treatment of RA and working under the supervision of a rheumatologist should initiate, supervise and assess response to treatment with rituximab.

Inadequate response or intolerance to biological DMARDs, and rituximab is not suitable
NICE TA195 Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of RA after the failure of a TNF inhibitor
NICE TA225; 2011: Golimumab for the treatment of RA after the failure of previous DMARDs
NICE TA247; 2012 Tocilizumab for treatment of RA
NICE TA415; 2016. Certolizumab pegol for treating RA after inadequate response to a TNF-alpha inhibitor
NICE TA466; 2017 Baricitinib for moderate to severe RA
NICE TA480; 2017 Tofacitinib for moderate to severe RA
NICE TA485;2017 Sarilumab for moderate to severe RA

- **Adalimumab, etanercept, infliximab**, **abatacept, certulizumab pegol, golimumab, and tocilizumab,** are recommended as treatment options in **combination with methotrexate** only in adults with:
  - severe active RA (DAS28 >5.1), **AND**
  - who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, **AND**
  - who cannot receive rituximab therapy because they have a CI to rituximab, or when rituximab is withdrawn because of an adverse event, **AND**
  - the companies provide certolizumab pegol, golimumab, and tocilizumab, as agreed in the PAS.
- **Adalimumab, etanercept, and certulizumab pegol,** are recommended as treatment options as **monotherapy** for adults with severe active RA; for people who cannot take methotrexate because of intolerance or it is CI and the criteria above are met.
- **Sarilumab**, in **combination with methotrexate**, is recommended as an option for treating active RA in adults:
  - whose disease has responded inadequately to DMARDs including at least one biological DMARD, **AND**
  - disease is severe (DAS28 >5.1), **AND**
  - who cannot receive rituximab therapy because they have a CI to rituximab, or when rituximab is withdrawn because of an adverse event, **AND**
  - the company provides sarilumab with the discount agreed in the PAS.
- **Sarilumab** can be used as **monotherapy** for people who cannot take methotrexate because of intolerance or it is CI and the criteria above are met.

Other immunomodulatory therapies
NICE TA480; 2017 Tofacitinib for moderate to severe RA
NICE TA466; 2017 Baricitinib for moderate to severe RA

- **Tofacitinib and baricitinib**, are recommended as treatment options **in combination with methotrexate** for treating active RA in adults:
  - whose disease has responded inadequately to DMARDs including at least one biological DMARD, **AND**
  - disease is severe (DAS28 >5.1), **AND**
  - they cannot have rituximab therapy**, AND**
  - the company provides tofacitinib and baricitinib as agreed in the PAS.
- **Tofacitinib** and **baricitinib**,can be used as **monotherapy** for treating active RA in adults who cannot take methotrexate because of intolerance or it is CI when the criteria above are met.

Inadequate response to rituximab and other biological DMARDS
- **Sarilumab** is recommended as a treatment option **in combination with methotrexate** for treating active RA in adults whose disease has responded inadequately to rituximab and at least one biological DMARD, only if:
  - disease is severe (DAS28 >5.1), **AND**
  - the company provides sarilumab with the discount agreed in the PAS.
- **Tocilizumab** is recommended as a treatment option in **combination with methotrexate** for treating RA in adults if:
  - the disease has responded inadequately to one or more TNF inhibitor treatments and to rituximab, **AND**
  - the manufacturer provides tocilizumab with the discount agreed in the PAS.

Resources
NICE RA management and monitoring algorithm

NICE RA referral, diagnosis and investigations algorithm

British Society for Rheumatology.
BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Rheumatology 2017;Vol 56 (6): 865–868, **www.rheumatology.org.uk/Knowledge/Excellence/Guidelines#guidelines**

Clinical Knowledge Summaries: DMARDS at **www.cks.nice.org.uk/dmards**

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