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Disease remission the goal of therapy in rheumatoid arthritis

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Cimmino MA et al. Genoa University, Italy. R&D Center for Imaging of Arthropathies. Courtesy EULAR image databank

Conventional radiography of the hands of a woman with long-standing rheumatoid arthritis. The 2nd and 3rd metacarpophalangeal joints of the left hand have been replaced by prostheses. Early diagnosis and treatment should make this type of case a thing of the past

Why is early diagnosis important?

RHEUMATOID ARTHRITIS WAS PREVIOUSLY CONSIDERED A SEVERE SYSTEMIC DISEASE leading to inexorable decline. However, the outlook for patients has altered dramatically over the past few years with disease remission now the therapeutic goal.

This is dependent on a number of critical interventions and the role of the GP is pivotal in the process. Without early recognition and rapid referral by the GP the ability to achieve the desired outcome of disease remission would be greatly hindered. A recent article in this journal highlighted the benefits of intensive therapy with tight control of disease.[1]

How should RA be classified?

DIAGNOSIS

In order to achieve remission, rapid diagnosis of rheumatoid arthritis is a key priority. It has long been recognised that the 1987 American College of Rheumatology (ACR) criteria for the classification of rheumatoid arthritis were inadequate for patients presenting with features of early disease. These criteria were originally developed to identify patients with established disease to include in clinical trials.

A profound and far-reaching change occurred when a new classification system for RA was published earlier this year (see table 1, p18). One of the great benefits of this innovative system is that it allows a diagnosis of RA to be made much earlier than previously. The criteria focus on clinical, biochemical and immunological features associated with persistent and/or erosive disease. As the condition has been redefined physicians now have the means to avoid the undesirable consequences of late diagnosis and treatment delay.

Why should patients be treated to target?

REFERRAL

Following presentation to primary care, patients with symptoms and signs of an inflammatory arthritis should be referred to a rheumatologist. This imperative has been highlighted in the NICE guideline on the treatment of RA.[2] The guideline recommends that any patient with suspected »

persistent synovitis of undetermined cause should be referred for specialist opinion and suggests urgent referral if any of the following apply:

- the small joints of the hands or feet are affected
- >1 joint is affected
- there has been a delay of >3 months between onset of symptoms and seeking medical advice

The basis for this advice lies in the observation that early disease is more amenable to intervention. A window of opportunity exists whereby early treatment results in a greater chance of inducing remission.[3] Ideally, this should be within six weeks of symptom onset. As a proportion of patients who develop severe persistent inflammatory arthritis will have normal investigations at disease onset (e.g. rheumatoid factor, anti-CCP antibodies, ESR, CRP and X-rays) they should be referred regardless. Similarly the referral should not be delayed pending investigations.

MANAGEMENT

A multidisciplinary approach to the management of rheumatoid arthritis is of course essential. In addition, lifestyle measures form an integral part of the treatment strategy. Smoking cessation for example is crucial as continued smoking may exacerbate inflammatory arthritis, make it harder to treat, and worsen the patient's cardiovascular risk profile.[4]

Traditional disease modifying antirheumatic drugs (DMARDs)

A fundamental shift in the approach to treating rheumatoid arthritis has occurred with the archaic 'start low, go slow' management pyramid having been resoundingly rejected. Currently one therapeutic tactic is to use combination DMARD therapy, incorporating methotrexate (MTX) with corticosteroids, at the outset.[5] This approach may not only achieve our aim of disease remission in early disease but also confer substantial clinical and radiographic benefit in established disease. This is reflected in the NICE guideline which suggests DMARD combinations initiated as first-line treatment as soon as possible.

Recently published European League against Rheumatism (EULAR) guidelines reinforce the early intensive treatment strategy. EULAR recommends initiating traditional DMARDs as soon as the diagnosis of rheumatoid arthritis is made aiming to achieve the target of remission or low

Table 1

The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis

Target population (who should be tested?)	
1 Patient has at least 1 swollen joint with definite clinical synovitis (swelling)	
2 Synovitis is not better explained by another disease	
Differential diagnoses differ in patients with different presentations but may include conditions such as systemic lupus erythematosus, psoriatic arthritis and gout. If unclear about the relevant differentials, an expert rheumatologist should be consulted	
Classification criteria for RA (Score-based algorithm: add score of categories A-D) A score of ≥ 6/10 is needed for a definite classification of a patient with RA	
A Joint involvement[1]	
1 large[2] joint	0
2-10 large joints	1
1-3 small[3] joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints[4] (at least one small joint)	5
B Serology[5] (at least one test result is needed for classification)	
Negative RF AND negative ACPA	0
Low positive RF OR low positive ACPA	2
High positive RF OR high positive ACPA	3
C Acute phase reactants[6] (at least one test result is needed for classification)	
Normal CRP AND normal ESR	0
Abnormal CRP OR abnormal ESR	1
D Duration of symptoms[7]	
<6 weeks	0
≥6 weeks	1

1 Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints (DIPs), 1st carpo-metacarpal (CMC) joint, and 1st metatarso-phalangeal (MTP) joint are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of the involved joints, with placement into the highest category possible based on the pattern of joint involvement

2 Large joints refer to shoulders, elbows, hips, knees and ankles

3 Small joints refer to the wrists, metacarpo-phalangeal (MCP) joints, proximal interphalangeal (PIP) joints, thumb interphalangeal (IP) joints and metatarsophalangeal (MTP) joints 2-5

4 In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g. temperomandibular, acromioclavicular and sternoclavicular joints)

5 Negative refers to international unit (IU) values that are ≤ upper limit of normal (ULN) for the lab and assay.
Low titre refers to IU values that are > ULN but ≤ 3 x ULN for lab and assay.
High titre positive: > 3 x ULN for lab and assay.
Where RF is only available as positive or negative, a positive result should be scored as 'low positive' for RF

6 Normal/abnormal is determined by local laboratory standards (Other causes for elevated acute phase reactants should be excluded)

7 Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g. pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status

RF = rheumatoid factor; **ACPA** = anti-citrullinated protein/peptide antibodies; **ESR** = erythrocyte sedimentation rate; **CRP** = C-reactive protein

Adapted from Aletaha D et al. 2010 Rheumatoid Arthritis Classification Criteria. An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. *Arthritis and Rheumatism* 2010;62:2569-81

Table 2

EULAR recommendations for the management of rheumatoid arthritis

1 Treatment with synthetic DMARDs should be started as soon as the diagnosis of RA is made
2 Treatment should be aimed at reaching a target of remission or low disease activity as soon as possible in every patient; as long as the target has not been reached, treatment should be adjusted by frequent (every 1-3 months) and strict monitoring
3 MTX should be part of the first treatment strategy in patients with active RA
4 When MTX contraindications (or intolerance) are present, the following DMARDs should be considered as part of the (first) treatment strategy: leflunomide, sulfasalazine or injectable gold
5 In DMARD naïve patients, irrespective of the addition of glucocorticoids (GCs), synthetic DMARD monotherapy rather than combination therapy of synthetic DMARDs may be applied
6 GCs added at low to moderately high doses to synthetic DMARD monotherapy (or combinations of synthetic DMARDs) provide benefit as initial short-term treatment, but should be tapered as rapidly as clinically feasible
7 If the treatment target is not achieved with the first DMARD strategy, addition of a biologic DMARD should be considered when poor prognostic factors are present; in the absence of poor prognostic factors, switching to another synthetic DMARD should be considered
8 In patients responding insufficiently to MTX and/or other synthetic DMARDs with or without GCs, biologic DMARDs should be started; current practice would be to start a TNF inhibitor (adalimumab, certolizumab, etanercept, golimumab, infliximab) which should be combined with MTX
9 Patients with RA for whom a first TNF inhibitor has failed, should receive another TNF inhibitor, abatacept, rituximab or tocilizumab
10 In cases of refractory severe RA or contraindications to biologic agents or the previously mentioned synthetic DMARDs, the following synthetic DMARDS might also be considered, as monotherapy or in combination with some of the above: azathioprine, ciclosporin A (or exceptionally, cyclophosphamide)
11 Intensive medication strategies should be considered in every patient, although patients with poor prognostic factors have more to gain
12 If a patient is in persistent remission after having tapered GCs, one can consider tapering biologic DMARDS, especially if this treatment is combined with a synthetic DMARD
13 In cases of sustained long-term remission, cautious titration of synthetic DMARD dose could be considered, as a shared decision between patient and doctor
14 DMARD naïve patients with poor prognostic markers might be considered for combination therapy of MTX plus a biologic agent
15 When adjusting treatment, factors apart from disease activity such as progression of structural damage, comorbidities and safety concerns should be taken into account

Adapted from Smolen JS, Landewé R, Breedveld FC et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010; 69:964-75

disease activity as rapidly as possible in every patient (see table 2, left).

MTX remains the 'anchor drug' for patients with active disease and where contraindications to MTX exist, or intolerance develops, another DMARD such as leflunomide or sulfasalazine should be considered as part of the first treatment strategy. Once prolonged and satisfactory levels of disease control have been achieved, doses may be cautiously reduced to levels that still maintain control.

Biologic DMARDs

Over the past decade the introduction of biologic therapies has led to a therapeutic revolution. The benefits have been manifold including improving the signs and symptoms of disease, radiographic progression, functionality, quality of life and even mortality. Eight biologic agents are currently available for the treatment of rheumatoid arthritis (see table 3, p20) with many more in development.

The EULAR guidelines state that if the treatment target is not achieved following the first traditional DMARD strategy, in the presence of poor prognostic factors, or in patients responding insufficiently to DMARDs, then biologic therapy should be considered. Current practice would be to start a TNFα inhibitor in combination with MTX. In patients with significant disease activity and/or risk factors for progressive disease e.g. rheumatoid factor or positivity to anti-CCP antibodies and high CRP, induction with biologics and maintenance with traditional DMARDs is another potential therapeutic strategy.

Currently in England and Wales, NICE states that to be eligible for biologic drugs, patients with rheumatoid arthritis should have a baseline disease activity score 28 (DAS-28) >5.1 (reflecting high disease activity), sustained over two points, one month apart, despite an adequate trial of at least two DMARDs (of which one should be MTX).[6] This hurdle is high and does not reflect the available evidence. The British Society for Rheumatology recently revised their eligibility criteria for rheumatoid arthritis patients starting their first biologic agent advocating introduction of these agents earlier in the treatment paradigm, in line with Europe and the USA.[7] It is hoped that this document will influence NICE during their next review of biologic therapy for rheumatoid arthritis.

Recent guidance from NICE »

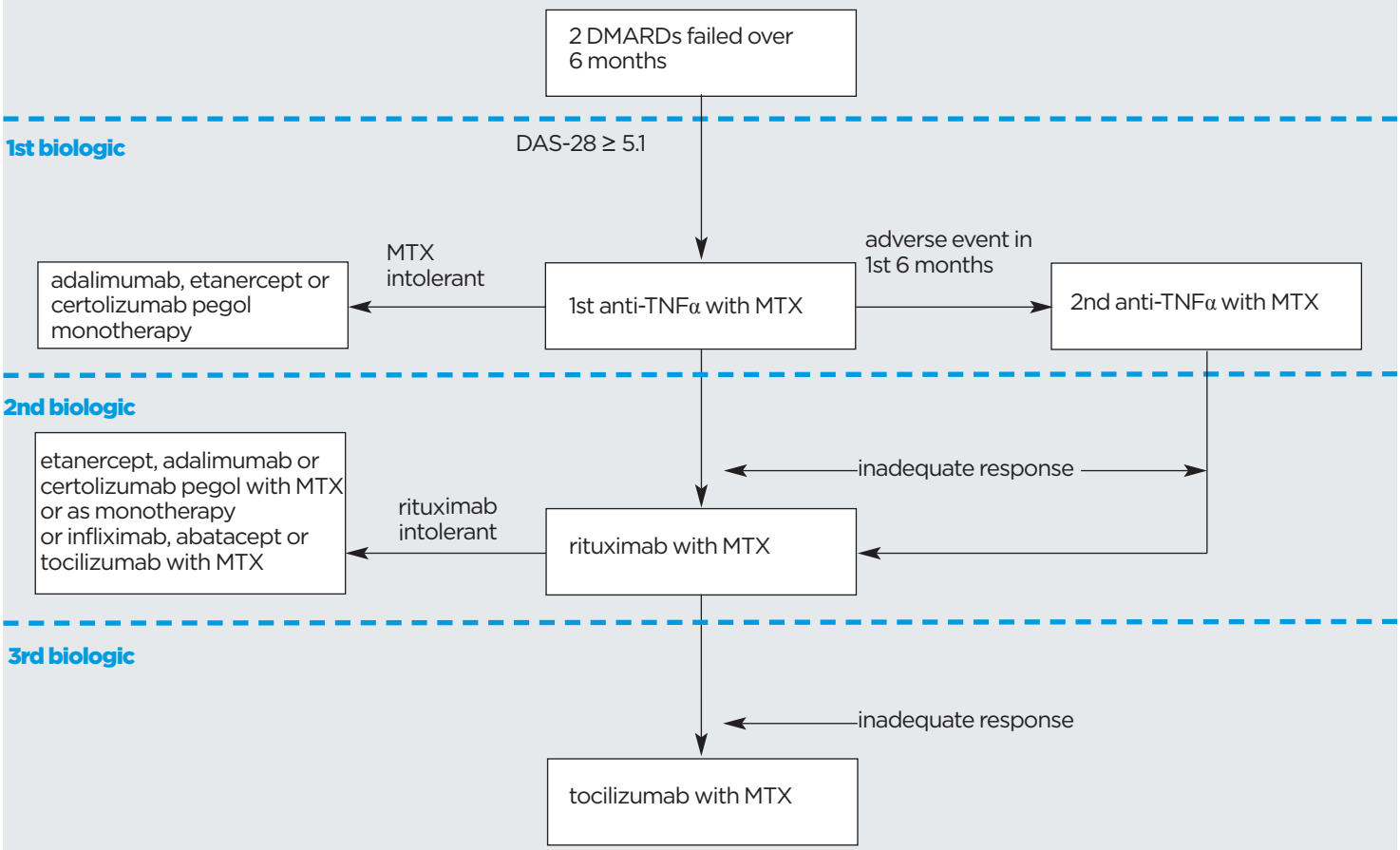
Table 3

Biologic drug treatments

Drug	Chemical structure	Half life	Dosage	Approved by NICE
Etanercept	Recombinant human soluble TNFα receptor fusion protein	70-132 hr	25 mg twice weekly or 50 mg weekly SC	Yes
Infliximab	Chimeric monoclonal antibody to TNFα	9.5 days	3 mg/kg repeated 2 weeks and 6 weeks after the first infusion, then every 8 weeks	Yes
Adalimumab	Recombinant human monoclonal antibody to TNFα	10-20 days	40 mg SC fortnightly	Yes
Abatacept	T cell co-stimulation blocking fusion protein	13 days	500-1000 mg (weight dependent) IV at 0, 2 & 4 weeks then monthly	Yes
Rituximab	Chimeric monoclonal antibody against CD20 (B cell depleting therapy)	19-22 days	Two 1 g IV doses two weeks apart then as symptoms dictate	Yes
Tocilizumab	IL-6 receptor inhibiting monoclonal antibody	6-10 days	8 mg/kg IV monthly	Yes
Golimumab	Fully human monoclonal antibody to TNFα	7-20 days	50 mg SC monthly	Pending
Certolizumab pegol	Pegylated recombinant humanised anti-TNFα antibody Fab fragment	14 days	400 mg SC at 0, 2 & 4 weeks then 200 mg fortnightly	Yes

Figure 1

A simplified overview of NICE guidance on biologics in rheumatoid arthritis



key points

SELECTED BY

Dr Peter Saul
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In order to achieve remission, rapid diagnosis of rheumatoid arthritis (RA) is a key priority. The new RA classification system allows a diagnosis to be made much earlier than previously. The criteria focus on clinical, biochemical and immunological features associated with persistent and/or erosive disease. Following presentation to primary care, patients with symptoms and signs of an inflammatory arthritis should be referred to a rheumatologist.

Any patient with suspected persistent synovitis of undetermined cause should be referred for specialist opinion and urgent referral if any of the following apply: the small joints of the hands or feet are affected; >1 joint is affected; there has been a delay of >3 months between onset of symptoms and seeking medical advice.

Early treatment results in a greater chance of inducing remission. Ideally, this should be within 6 weeks of symptom onset. Patients who develop severe persistent inflammatory arthritis who have normal investigations at disease onset should be referred regardless. Similarly, referral should not be delayed pending investigations.

Lifestyle measures form an integral part of the treatment strategy. A fundamental shift in the approach to treating RA has occurred with the archaic 'start low, go slow' management pyramid having been rejected. One tactic is to use combination DMARD therapy, incorporating methotrexate with corticosteroids, at the outset.

EULAR recommends initiating traditional DMARDs as soon as the diagnosis of RA is made aiming to achieve the target of remission or low disease activity as rapidly as possible. Once prolonged and satisfactory levels of disease control have been achieved, drug doses may be cautiously reduced to levels that still maintain disease control.

EULAR guidelines state that if the treatment target is not achieved following the first traditional DMARD strategy, in the presence of poor prognostic factors, or in patients responding insufficiently to DMARDs, then biologic therapy should be considered. NICE states that to be eligible for biologic drugs, patients with RA should have a baseline DAS-28 score reflecting high disease activity, sustained over two points, one month apart, despite an adequate trial of at least two DMARDs (of which one should be MTX). This hurdle is high and does not reflect the available evidence. The BSR recently revised their eligibility criteria for RA patients starting their first biologic agent advocating introduction of these agents earlier in the treatment paradigm, in line with Europe and the USA.

Treatment with a biologic requires strict monitoring under the guidance of a specialist. GPs should become familiar with these drugs as their use is increasing in rheumatology and other disciplines. Evidence now supports tight disease control, specifically inflammation, by reviewing the patient regularly and adjusting medications until a predefined target is achieved.

addresses the newest biologic agent tocilizumab[8] and the therapeutic approach to adopt in those patients who have not responded to their first anti-TNFα agent.[9] In essence following an inadequate response or intolerance to an initial TNFα antagonist the options include switching to an alternative TNFα inhibitor or rituximab (or abatacept or tocilizumab if rituximab is contraindicated, see figure 1, opposite). Each agent has its benefits and limitations thus the decision as to which to use depends predominantly on patient factors such as seropositive or seronegative disease, systemic features, and the ability to tolerate MTX. A detailed discussion of this is beyond the scope of this article.

It should be noted that treatment with a biologic requires strict monitoring under the guidance of a specialist in the area. GPs, however, should become familiar with these drugs as their use is increasing not only in rheumatology but in many other disciplines.

Treatment to target

Historically patients with rheumatoid arthritis have been reviewed every three to six months with treatment altered on an ad hoc basis. This often left patients with active disease for several months or longer resulting in progressive joint damage.

Considerable evidence now supports tight control of disease, specifically of inflammation, by reviewing the patient regularly and adjusting medications accordingly until a predefined target, such as remission or low disease activity, is achieved.[10] The DAS-28 is the tool available for the clinician to monitor the activity of rheumatoid arthritis and thus alter treatment.[11] Our mantra is the lower the DAS-28 the better!

As a consequence the treat to target initiative developed recommendations to promote and provide guidance on methods to achieve this ideal.[12] The technique has been borrowed from other areas in medicine where target-driven therapy results in improved outcomes e.g. lipid and blood pressure control in cardiology and HbA_{1c} control in diabetes. Similarly, tight control of rheumatoid arthritis improves all aspects of disease including joint damage and quality of life.

The treat to target recommendations closely mirror other guidelines for the desirability of intensive intervention at any stage of rheumatoid arthritis to reduce the inflammatory burden as comprehensively as possible. These strategies will ensure that treatment is escalated rapidly to maximise the patient's potential.

CONCLUSION

A number of significant advances have been made in the past few years in the management of rheumatoid arthritis. We are now in a position to alter the natural history of the disorder profoundly with the goal of therapy being disease remission. This has largely been a consequence of the shift in the treatment paradigm focusing on early intensive therapy, algorithm-driven management with tight control, and the introduction of biologic therapies. The role of the GP is critical in identifying patients early and referring rapidly which will only result in greatly improved outcomes for our patients.

REFERENCES

1 Östör AJ, Conaghan PG. Tight control in rheumatoid arthritis improves outcomes. *Practitioner* 2009; 253 (1716):29-32
2 National Institute for Health and Clinical Excellence CG79. Rheumatoid arthritis: The management of rheumatoid arthritis in adults. NICE. London. 2009
3 Cush JJ. Early rheumatoid arthritis -- is there a window of opportunity? *J Rheumatol Suppl* 2007;80:1-7
4 Masdottir B, Jonsson T, Manfredsdottir V et al. Smoking, rheumatoid factor isotypes and severity of rheumatoid arthritis. *Rheumatology* 2000;39(11):1202-5
5 Korpela M, Laasonen L, Hannonen P et al. Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study. *Arthritis and Rheumatism* 2004;50(7):2072-81
6 National Institute for Health and Clinical Excellence. TA130. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. NICE. London. 2007
7 Deighton C, Hyrich K, Ding T et al. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. *Rheumatology* 2010;49:1197-9
8 National Institute for Health and Clinical Excellence. TA198. Rheumatoid arthritis: tocilizumab. NICE. London. 2010
9 National Institute for Health and Clinical Excellence. TA195. Rheumatoid arthritis: drugs for treatment after failure of a TNF inhibitor. NICE. London. 2010
10 Grigor C, Capell H, Stirling A et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004;364(9430):263-9
11 Fransen J, van Reil PL. The Disease Activity Score and the EULAR response criteria. *Clin Exp Rheumatol* 2005;23:S93-9
12 Smolen JS, Aletaha D, Bijlsma JW et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010; 69: 631-637

Useful information

British Society for Rheumatology
www.rheumatology.org.uk
European League Against Rheumatism
www.eular.org
Arthritis Research UK
www.arthritiscare.org.uk
National Rheumatoid Arthritis Society
www.nras.org.uk