Treat to Target Approach in Rheumatoid Arthritis: UK perspective

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What is the target?

To achieve remission or low disease activity in Rheumatoid Arthritis
Why has Treat to Target in RA evolved?

because the traditional approach, while suppressing some of the inflammation, does not stop the progressive joint damage and development of disability
traditional approach...

- patients were treated symptomatically

- referral to a specialist team was delayed

- Disease Modifying Anti-Rheumatic Drugs (DMARDS), were introduced only if:

  1) *symptomatic treatment failed or was not tolerated*

  2) *joint erosion was evident on X-ray*

  3) *extra-articular complications developed*
traditional approach...

*like shutting the door after the horse has bolted*

- achieved symptom control BUT radiological damage and disability progressed and extra-articular complications were common

- after 1 year of DMARD therapy, joint erosions were seen in 30%

- after 2 years of DMARD therapy joint erosions were seen in 70%

- complete remission occurred in only 2% after 3 years
inflammation, disability, radiological damage

Duration of Disease (years)

Severity

What has changed?

A combination of factors have led to a re-evaluation of the approach to treating Rheumatoid Arthritis:

• the introduction of biological agents in 1998

• an understanding that treatment early in disease reduces joint damage

• evidence emerged that DMARDs used in combination rather than as monotherapy produced better results

• availability of more sophisticated imaging, U/S and MRI, to help with earlier diagnosis and assessment of treatment
early introduction of treatment

• data from many studies shows that if we intervene early with effective therapy, thereby achieving low disease activity or remission, structural damage to joints is limited and the longer term co-morbidities avoided
Importance of Early Referral

“Window of opportunity”: time-frame during which optimal treatment will yield the best outcome resulting in long-term sustained benefits

Regardless of DMARD used, clinical responses were consistently better when the DMARD was used earlier in disease

From Cush J. J Rheum 2007;34:suppl 80.

The Sharp Score is a radiographical assessment of changes in total joint damage as assessed by bone erosions and joint space narrowing

Leiden early arthritis clinic

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combination therapy...

- COBRA study compared combination of MTX (7.5mg/week) with SZP (2gm/day) and high dose steroid 60mg/day (tapered every 6 weeks and stopped at 6 months) with

- SZP alone

combination group showed fewer erosions and less disability
Early Aggressive Therapy Provides for Long-term Results

Damage Progression (Sharp/van der Heijde)

SSZ: 8.6 points/y

COBRA: 5.4 points/y

P = 0.008

BeST study 2005

2 year follow results from Dutch study (508 patients with disease <2 years) compared:

- sequential monotherapy (gp 1)
- step up combination therapy (gp 2)
- initial combination therapy with tapered high dose prednisolone (gp 3)
- initial combination therapy with infliximab (gp 4)

Combination therapies (groups 3 and 4) resulted in more rapid clinical and functional outcome and lower risk of having progressive disease. There was no significant difference between adverse events and withdrawals between the groups.

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Treat to Target – Principles and Recommendations
International Steering Committee

- Treat to Target Steering Committee was chaired by Professor Josef Smolen
- A task force of rheumatologists and a patient developed set of recommendations on the basis of evidence derived from a systematic literature review and expert opinion
- These recommendations were subsequently discussed, amended and voted upon by >60 experts from various regions of the world in a Delphi-like procedure
- Levels of evidence, strength of recommendations and levels of agreement were derived
UK Treat to Target Steering Committee

- **Professor Paul Emery**, Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds
- **Dr Maya Buch**, Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds
- **Dr Cristina Estrach**, University Hospital Aintree, Liverpool
- **Dr Tim Jenkinson**, Royal National Hospital for Rheumatic Diseases, Bath
- **Dr Bruce Kirkham**, Guy's Hospital, Southwark, London
- **Dr Andrew Östör**, Rheumatology Clinical Research Unit at Addenbrooke's Hospital, Cambridge
- **Dr Duncan Porter**, Gartnavel General Hospital, Glasgow
- **Professor Peter Taylor**, Charing Cross Hospital, London
The Overarching Principles

A. The treatment of rheumatoid arthritis must be based on a shared decision between patient and rheumatologist.

B. The primary goal of treating the patient with rheumatoid arthritis is to maximise long term health-related quality of life through control of symptoms, prevention of structural damage, normalization of function and social participation.

C. Abrogation of inflammation is the most important way to achieve these goals.

D. Treatment to target by measuring disease activity and adjusting therapy accordingly optimises outcomes in rheumatoid arthritis.
Algorithm to Treat RA to Target

1. Active RA
   - Adapt therapy according to disease activity
   - Use a composite measure of disease activity every 1-3 months

2. Remission
   - Assess disease activity about every 3-6 months
   - Adapt therapy if state is lost

3. Sustained Remission
   - Sustained low disease activity
   - Adapt therapy if state is lost

4. Low disease activity
   - Alternative target
   - Adapt therapy according to disease activity

Main target
DAS28: Calculation and Interpretation

- DAS28 provides a number on a scale from 0 to 10 which indicates the current activity of the disease.

Scores can be classified as:\(^1,^2\)
- Remission: DAS28 < 2.6
- Low: DAS28 ≤ 3.2
- Moderate: 3.2 < DAS28 ≤ 5.1
- High: DAS28 > 5.1

Algorithm to Treat RA to Target\(^1\)

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3. **Low disease activity**
   - Adapt therapy according to disease activity

4. **Sustained Remission**
   - Adapt therapy if state is lost
   - Sustained low disease activity

5. **Main target**

Alternative target
Treat to Target in Rheumatology Key Points

- **TARGET:** Set and record a target. This should be clinical remission, but in exceptional cases it may be low disease activity.

- **ASSESSMENT:** Regularly assess disease activity using validated composite measures of disease activity that include joint assessments (such as DAS28) – up to monthly in patients with high/moderate disease and 3–6 months for patients with sustained low disease activity or remission.

- **TREATMENT:** Adjust at least every 3 months until the target is reached.

- **PATIENT INVOLVEMENT:** Agree and set targets with the patient and involve the patient in treatment decisions and their management plan.
How do we achieve T2T for RA

• audit of service

• education for primary care physicians and hospital colleagues

• early arthritis clinics

• optimising use of assessment tools eg diagnostic ultrasound
• People with RA visit a GP on average four times before being referred to a specialist for diagnosis, and 18% visit more than eight times.
• Clinical monitoring is not yet routinely carried out for all people with rheumatoid arthritis. At the time of census (Jan 2009):
  • Only 63% of acute trusts reported that they were offering all patients an annual review
  • Only 15% of trusts reported that they were offering all patients with active disease a monthly review
• The NAO report recommends:
  • Improving awareness in primary care, including how to recognise the symptoms of inflammatory arthritis and the need to refer suspected cases promptly, so that any delay from onset of symptoms to treatment is minimised
UK Treat to Target steering committee audit

- conducted when T2T guidelines were published in 2009
- found that there were shortcomings

A defined treatment target is not routinely set in clinical practice

Composite measure (DAS28)/alternative could be applied more systematically

There exists scope for more stringent DMARD escalation

There is an ongoing need for still more effective/efficient referral

Work instability documentation should be more formally/regularly documented
Early Arthritis Clinic

- many set up in the UK
- best way to process referrals
- need extra manpower
- imaging with portable ultrasound can be incorporated
Early Arthritis Clinic referral

Patients will be eligible for the EAC if they meet the following criteria (✔ all that apply):

• Arthritic Symptoms present for at least 4 weeks but less than 1 year
• Early morning stiffness lasting more than 30 mins

AND ANY ONE OF THE FOLLOWING:

• 3 or more swollen joints

• Tender/involved metacarpophalangeal joints

• Tender/involved metatarsophalangeal joints
Assessment tools

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Assessment and DAS28

- All clinicians and nurses who see patients should be trained to conduct DAS28.
- DAS28 should be performed and scored every time a patient visits the clinic.
- A target DAS score should be set once the baseline score is taken.
- Assessment should include setting a realistic personal target for the patient.

Training manual available in toolkit.
Ultrasound/MRI
Diagnostic ultrasound versus MRI

- they are not rivals; both are useful for diagnosis and assessment of on-going disease activity in RA, showing synovitis and erosive change.

- MRI is more expensive but less operator dependent and is better for showing effects on bone, such as bone oedema.

- ultrasound is cheaper and can be available to the clinician in the outpatient department but is more operator dependent. It takes less time to do and avoids ionising irradiation. Examination of multiple joints is possible.
MRI

- Bone marrow oedema may precede the development of bone erosions and can be used to predict medium-term functional disability.

- It is detectable with STIR T2-weighted or fat-suppressed T2-weighted MRI sequences.

- Bone marrow oedema appears as a lesion with ill-defined margins and high signal intensity, typically located at the insertion of the synovial membrane. It can occur alone, or it may surround bone erosions.

- In contrast to MRI, sonography provides no information on bone marrow oedema.
34-year-old woman with early rheumatoid arthritis and synovitis. Transverse fat-suppressed gadolinium-enhanced T1-weighted spin-echo MR images show bilateral synovitis (*arrows*) in wrist (A) and metatarsophalangeal joints (B). Note also bone marrow signal intensity changes (*asterisks, B*), which precede frank bone erosions, and flexor digitorum tenosynovitis (*arrowhead, A*).
more recently, methods of semiquantitative scoring of early rheumatoid arthritis changes at the wrist and MCP joints have been developed and standardized on MRI by the OMERACT (Outcome Measures in Rheumatology Clinical Trials) and EULAR (European League Against Rheumatism) groups.

similar work is underway with diagnostic ultrasound
Diagnostic Ultrasound in RA

• diagnostic U/S is becoming an increasingly valuable tool in diagnosis and treatment of RA

• Access to a portable U/S machine in the outpatient clinic is ideal

• Power doppler assists greatly in the detection of active disease
- 29-year-old woman with early rheumatoid arthritis and tenosynovitis. R = radius, U = ulna, t = tendon. Dorsal transverse sonogram of wrist shows hypoechoic thickening (asterisks) and hyperaemia around extensor carpi ulnaris tendon on power Doppler imaging, representing tenosynovitis. Note also heterogeneous appearance of tendon on sonography.
47-year-old woman with rheumatoid arthritis and bone erosions. Coronal sonogram of hand shows hypervascular pannus filling bone erosion (arrows) on radial aspect of second metacarpal bone (M2) on power Doppler imaging. Note also hyperemia in articular space.
• the 2012 update of 2008 ACR recommendations for “Treat to Target” statements says:

• The primary target is clinical remission, with no signs or symptoms of inflammation

• How do we define remission, in clinical or imaging terms?
Imaging remission?

• Imaging studies using MRI and diagnostic ultrasound show that many patients, who are defined as being in remission clinically, still have evidence of synovitis on imaging.

• It is now known that these patients will continue to progress in terms of joint damage.

• So, ideally, remission needs to be defined in imaging terms.
U/S problems

• training rheumatologists is difficult

• the portable machines are expensive

• there is not time in a busy clinic to do ultrasound as well
What can help

• Targeted Ultrasound Initiative (TUI)

• TUI is an international network dedicated to promoting the use of U/S in the management of RA, and to increase the understanding of the role of U/S in improving patient outcomes

• UK ambassador is Christina Estrach, in Liverpool

• TUI seeks to promote education, research and training in U/S for RA

• Currently working on standardising U/S findings by a grading system for synovitis (grades 1-3)
Cost benefits of T2T for RA

• Tight control needed for T2T can achieve remission or low disease activity, without the use of biological agents

• Cost of treatment can therefore be reduced
Intensive (vs Routine) RA Management Improves Patient-centred Outcomes at No Extra Cost\(^1\)

- Intensive outpatient management of RA substantially improves disease activity, radiographic disease progression, physical function and quality of life at no additional cost.

![Graph showing disease activity score over months for intensive and routine management.]

Mean disease activity score, intensive vs routine after month 3, \(p<0.0001\). Error bars show SD.

![Bar chart comparing hospital and community costs for routine and intensive management.]

conclusions

• Treat to Target for RA is the only way forward if we are to minimise the effects of this serious disease which can have devastating effects on the life of an individual, in terms of disability, unemployment, considerable co-morbidity and shortened life expectancy
Thankyou