Drug selection in Rheumatoid Arthritis

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Rheumatoid arthritis

- Autoimmune disease
- Onset generally occurs between 30 and 55 years of age
- Women are affected more often than men.
Disease hallmarks

- Inflammation of the synovium
- Progressive bone erosion
- Joint malalignment and destruction, and
- Weakness of surrounding tissues and muscles.
Presentations range from mild to severe
Progressive course leading to functional limitations.
RA-Pathophysiology
Principles of treatment of RA

- Early diagnosis and commencement with DMARD treatment
- Alleviating or minimising pain
- Stopping the disease process
- Preventing deformity
- Minimising functional loss
- Regular monitoring for drug efficacy and toxicity
- Active patient participation in management of the condition.

The Rheumatology Expert Group 2006
Treatment options in RA
Drug treatment in RA

- NSAIDS & Analgesics
- Corticosteroids
- DMARDs
  - Synthetic DMARDs
    1. Methotrexate
    2. Hydroxychloroquine
    3. Sulfasalazine
    4. Leflunomide
    5. Minocycline
  - Biologic DMARDs
    - Non-TNF
      1. Abatacept
      2. Rituximab
      3. Tocilizumab
    - Anti-TNF
      4. Adalimumab
      5. Etanercept
      6. Infliximab
      7. Certolizumab pegol
      8. Golimumab
Indications for starting, resuming, adding, or switching DMARDs or biologic agents

- Target low disease activity or remission
<table>
<thead>
<tr>
<th>Measure</th>
<th>Remission</th>
<th>Low activity</th>
<th>Moderate activity</th>
<th>High activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Activity Scale (PAS) or PAS-II (range 0–10)</td>
<td>0–0.25</td>
<td>0.26–3.7</td>
<td>3.71 to 8.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Routine Assessment of Patient Index Data 3 (range 0–10)</td>
<td>0–1.0</td>
<td>1.0 to 2.0</td>
<td>2.0 to 4.0</td>
<td>4.0 to 10</td>
</tr>
<tr>
<td>Clinical Disease Activity Index (range 0–76.0)</td>
<td>2.8</td>
<td>2.8 to 10.0</td>
<td>10.0 to 22.0</td>
<td>22</td>
</tr>
<tr>
<td>Disease Activity Score in 28 joints (range 0–9.4)</td>
<td>2.6</td>
<td>2.6 to 3.2</td>
<td>3.2 to 5.1</td>
<td>5.1</td>
</tr>
<tr>
<td>Simplified Disease Activity Index (range 0–86.0)</td>
<td>3.3</td>
<td>3.3 to 11.0</td>
<td>11.0 to 26</td>
<td>26</td>
</tr>
</tbody>
</table>
Early RA (disease duration ≤ 6 months)

- DMARD monotherapy
- DMARD combination therapy (including double and triple therapy)
- Anti-TNF biologic with or without methotrexate
Established RA (disease duration 6 months or meeting the 1987 ACR RA classification criteria)

- Initiating and switching among DMARDs.
- Switching from DMARDs to biologic agents.
- Switching among biologic agents due to lack of benefit or loss of benefit.
- Switching among biologic agents due to harms/adverse events.
Early RA (disease duration $\leq$ 6 months)

DMARD monotherapy

- Low disease activity
- Moderate or high disease activity with the absence of poor prognostic features
Poor prognostic factors

Presence of 1 or more of the following features:

- Functional limitation (e.g., HAQ DI or similar valid tools),
- Extraarticular disease
  - Rheumatoid nodules,
  - RA vasculitis,
  - Felty’s syndrome
- Positive rheumatoid factor or anti-CCP antibodies, or
- Bony erosions by radiograph
DMARD combination therapy (including double and triple therapy)

- Moderate or high disease activity plus poor prognostic features
Anti-TNF biologic with or without methotrexate

- High disease activity with poor prognostic features
- Infliximab is the only exception and the recommendation is to use it in combination with methotrexate, but not as monotherapy.
Established RA (disease duration 6 months or meeting the 1987 ACR RA classification criteria)

Initiating and switching among DMARDs.

- After 3 months of DMARD monotherapy (in patients without poor prognostic features), deteriorates from low to moderate/high disease activity, then MTX, hydroxychloroquine, or leflunomide should be added.

- After 3 months of treatment with MTX or MTX/DMARD combination, moderate or high disease activity, add another non-MTX DMARD or switch to a different non-MTX DMARD.
Switching from DMARDs to biologic agents.

- Moderate or high disease activity after 3 months of MTX monotherapy or DMARD combination therapy switch to an anti-TNF biologic, abatacept, or rituximab.
- After 3 months of intensified DMARD combination therapy or after a second DMARD, still has moderate or high disease activity, add or switch to an anti-TNF biologic.
Switching among biologic agents due to lack of benefit or loss of benefit

- Moderate or high disease activity after 3 months of anti-TNF biologic therapy switch to another anti-TNF biologic or a non-TNF biologic
- Moderate or high disease activity after 6 months of a non-TNF biologic switch to another non-TNF biologic or an anti-TNF biologic
Switching among biologic agents due to harms/adverse events

- High disease activity after failing an anti-TNF biologic due to serious adverse event, switch to a non-TNF biologic
- Moderate or high disease activity after failing an anti-TNF biologic because of a nonserious adverse event, switch to another anti-TNF biologic or a non-TNF biologic
- Moderate or high disease activity after failing a non-TNF biologic because of an adverse event (serious or nonserious), switch to another non-TNF biologic or an anti-TNF biologic
Treatment of RA in Special situation
Use of biologic agents in RA patients with hepatitis, malignancy, or CHF, qualifying for more aggressive treatment

Hepatitis B or C

- Etanercept can be used in RA patients with hepatitis C requiring RA treatment
- Biologic agent contraindicated in
  - untreated chronic hepatitis B (disease not treated due to contraindications to treatment or intolerable adverse events) and
  - RA patients with treated chronic hepatitis B with Child-Pugh class B and higher
Malignancies

- Can start or resume any biologic agent
  - Patients who have been treated for solid malignancies or non-melanoma skin cancer more than 5 years ago

- Rituximab can only be used in RA patients with:
  - previously treated solid malignancy within the last 5 years,
  - previously treated nonmelanoma skin cancer within the last 5 years,
  - previously treated melanoma skin cancer, or
  - previously treated lymphoproliferative malignancies
CHF

- Anti-TNF biologic should not be used in RA patients with CHF with
  - New York Heart Association (NYHA) class III or IV and
  - who have an ejection fraction of 50% or less
TB screening for biologic agents

Screening should be done to identify Latent TB Infection in all RA patients being considered for therapy with biologic agents.
Vaccination in patients starting or currently receiving DMARDs or biologic agents

- Before starting a DMARD or a biologic agent patient should be vaccinated against with
  - all killed (pneumococcal, influenza intramuscular, and hepatitis B)
  - recombinant (human papillomavirus [HPV] vaccine for cervical cancer), and
  - live attenuated (herpes zoster)

- if not previously done vaccination is recommended as soon as possible
Pregnancy and RA

- In most patients with RA go into remission during pregnancy.
- **Conception**: methotrexate and leflunomide should be discontinued for at least 3 months before trying to conceive.
- Paracetamol: the oral analgesic of choice during pregnancy.
- Oral NSAIDs and selective COX-2 inhibitors: can be used after implantation up until the last trimester.
- Corticosteroids: to control disease flares; risk are hypertension, glucose intolerance and osteoporosis.
- Safe DMARDs: sulfasalazine, hydroxychloroquine, azathioprine or ciclosporin if required to control inflammation.
- Avoid DMARDs: methotrexate, leflunomide, cyclophosphamide, gold and penicillamine.
- Biological therapies: safety unclear.
- Breastfeeding: methotrexate, leflunomide, cyclophosphamide, ciclosporin, azathioprine, sulfasalazine and hydroxychloroquine are contraindicated.
ACR recommendation 2012

Early RA

- **Disease Activity**
  - Low
  - Moderate
  - High

- **Target Low Disease Activity or Remission**

- **Features of Poor Prognosis**†
  - Without
  - With

- **DMARD monotherapy**
  - **Combination DMARD therapy** (double and triple therapy)‡
  - **DMARD monotherapy** Or HCQ and MTX
  - **Anti-TNF with or without MTX** Or Combination DMARD therapy (double and triple therapy)‡
ACR recommendation 2012
EULAR recommendations 2013

Phase I

- No contraindication for methotrexate

Clinical diagnosis of rheumatoid Arthritis*

- Combine with short-term low dose glucocorticoids
- Start leflunomide or sulfasalazine, alone or in combination²

Start methotrexate or combination¹ of conventional synthetic DMARDs

Failure phase I: go to phase II

Achieve target within 6 months**

No → Continue
EULAR recommendations 2013

**Phase II**

- **Prognostically unfavourable factors present**
  - such as RF/ACPA, esp. at high levels; very high disease activity; early joint damage

- **Failure for lack of efficacy and/or toxicity in phase I**

- **Prognostically unfavourable factors absent**

- **Add a biologic agent**
  - TNF-inhibitor or Abatacept or Tocilizumab (Rituximab under certain conditions)

- **Achieve target within 6 months**

- **Change to a second conventional synthetic DMARD strategy**
  - Leflunomide, sulfasalazine, methotrexate alone or in combination (ideally with addition of glucocorticoids as above)

- **Failure phase II: go to phase III**

- **Achieve target within 6 months**

- **Yes** → Continue

- **No**

- **Achieve target within 6 months**

- **Yes** → Continue

- **No**
EULAR recommendations 2013
Low-dose glucocorticoids

▪ Should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible.

▪ Low dose refers primarily to a dose of 7.5 mg prednisone or equivalent per day
- Proven capacity to increase clinical, functional and structural efficacy when combined with csDMARDs
- Combination has similar efficacy when compared with TNF inhibitors plus MTX (COBRA)
- Lower doses extended over a year or two, may increase DMARD activity and are even effective in this regard as monotherapy
Monotherapy is not specifically recommended and should only be used in exceptional cases when all other DMARDs have contraindications.

Task Force suggests using them only as bridging therapy and limiting their use to a maximum of 6 months then ideally tapering them.
IMPROVED trial

- Very high rate of good outcomes using MTX plus low-dose glucocorticoids within a few months.

SAVE (Stop Arthritis Very Early) trial

- No efficacy of a single GC injection irrespective of added csDMARDs.
- Initial treatment of RA with low-dose prednisone plus MTX showed higher rates of remission and lower Health Assessment Questionnaire (HAQ) scores.

CAMERA II

- The MTX plus prednisone (10 mg/day) strategy was more effective than MTX plus placebo in reducing the progression of erosive joint damage.
- MTX plus prednisone attained sustained remission at an earlier time point than MTX alone.
- Need for additional treatment was significantly lower in the MTX plus prednisone group than in the MTX monotherapy group.
- There were no new safety concerns over 2 years beyond those previously reported.
Nonsteroidal anti-inflammatory drugs

- NSAIDs interfere with prostaglandin synthesis through inhibition of the enzyme cyclooxygenase (COX)
- Reduce swelling and pain
- Do not retard joint destruction
- Not sufficient to treat RA when used alone
- 6 placebo-controlled trials comparing celecoxib with placebo
- Risk of cardiovascular death, myocardial infarction, stroke, heart failure, or thromboembolic events increased after celecoxib treatment in a dose-dependent fashion
Analgesics

- Acetaminophen, tramadol, codeine, opiates, and various other analgesics can be used to reduce pain.
- These agents do not affect swelling or joint destruction.
Commonly used NSAIDs

- Ibuprofen
- Naproxen
- Ketoprofen,
- Piroxicam
- Indomethacine
- Diclofenac, and
- Selective COX 2 inhibitor- Celecoxib
SYNTHETIC DMARDs

- Methotrexate (MTX)
- Sulfasalazine (SSZ)
- Hydroxychloroquine (HCQ)
- Leflunomide (LEF)
- Minocycline
MTX

- First treatment strategy in patients with active RA.
- Highly effective as monotherapy and in combination with glucocorticoids, other csDMARDs and bDMARDs
- Anchor drug in RA
As monotherapy with or without glucocorticoids leads to low disease activity states or 70% improvement in 25-50% of patients with early RA within 6-12 months.

Some patients with low disease activity (defined as CDAI≤10, DAS28<3.2, SDAI≤11) may not need MTX and can do well on alternative csDMARD therapies;

Patients previously treated with other csDMARDs who should receive MTX at a sufficient dose and for sufficient time before progressing to potentially more intensive therapies.
Necessary steps when using MTX

- Dose optimization
- Optimal use of folic acid
- Recognition that the maximum effect of MTX is attained only after 4–6 months
- The optimal dose of 25-30 mg a week with folate substitution, should be maintained for at least 8 weeks
- When MTX is contraindicated (or early intolerance)

Leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy
Sulfasalazine

- SSZ monotherapy is recommended for patients with
  - all disease durations
  - without poor prognostic features and
  - with all degrees of disease activity


- Meta-analysis of 15 randomized clinical trials support the effectiveness of SSZ as a treatment for RA
  

- Reduction in erosions has been reported with SZZ
  
  **Van der Heijde D, Van Riel P, Nuver Swart I, GribnauF, Van de Putte L. Effects of Hydroxychloroquine and sulphasalazine on progression of joint damage in Rheumatoid arthritis. Lancet 1989;i:1036-8**

- No teratogenicity is reported from over 2000 reports of pregnancy on the drug
- The drug be should be discontinued in pregnancy unless considered essential because of severe disease.
- The drug is considered safe in lactation, with little SSZ in the milk

- **Day RO. Rheumatology. Klippel and Dieppe. Mosby publishers. 8.12. SAARDS**
Comparison between HCQ & SSZ

<table>
<thead>
<tr>
<th>Variable</th>
<th>SSZ</th>
<th>HCQ</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>lack of efficacy dropouts</td>
<td>5%</td>
<td>15%</td>
<td>p = 0.055</td>
</tr>
<tr>
<td>ESR</td>
<td>43%</td>
<td>26%</td>
<td>p = 0.10</td>
</tr>
<tr>
<td>Morning stiffness</td>
<td>59%</td>
<td>40%</td>
<td>p = 0.09</td>
</tr>
</tbody>
</table>
Hydroxychloroquine

- Milder drugs

- Chloroquine is generally used for milder disease or in combination therapy

- It takes about three to six months to demonstrate efficacy

- Double blind studies show efficacy in 60-80 percent of patients

- Regular 6 - 12 monthly eye checks for field-testing.

- Decrease disease activity of at least 30% has been described in up to 63% of patients.

There is no influence on erosion progression compared to SSZ

- Van der Heijde D, Van Riel P, Nuver Swart I, GribnauF, Van de Putte L. Effects of Hydroxychloroquine and sulphasalazine on progression of joint damage in Rheumatoid arthritis. Lancet 1989;i:1036-8
- Felson DT, Anderson JA, Meenan RF. The comparative efficacy and toxicity of second line drugs in rheumatoid arthritis. Results of 2 meta-analyses. 1990 Arthritis Rheum;33;10,1449-61

- 100 reports exist of pregnancy in rheumatoid arthritis patients on anti-malarials.
- No reports of adverse fetal effect

The combination of **MTX** and **HQ** was the most popular DMARDs prescribed in the US and Canada.

Leflunomide

1. Reduction of signs and symptoms
2. Inhibition of structural damage
3. Improvement in physical function
<table>
<thead>
<tr>
<th>Comparisons</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>US301</td>
<td>LEF vs. PL</td>
<td>(12, 32)</td>
</tr>
<tr>
<td></td>
<td>MTX vs. PL</td>
<td>(8, 30)</td>
</tr>
<tr>
<td></td>
<td>LEF vs. MTX</td>
<td>(-4, 16)</td>
</tr>
<tr>
<td>MN301</td>
<td>LEF vs. PL</td>
<td>(7, 33)</td>
</tr>
<tr>
<td></td>
<td>SSZ vs. PL</td>
<td>(4, 29)</td>
</tr>
<tr>
<td></td>
<td>LEF vs. SSZ</td>
<td>(-8, 16)</td>
</tr>
<tr>
<td>MN302</td>
<td>LEF vs. MTX</td>
<td>(-19, -7)</td>
</tr>
</tbody>
</table>
No consistent differences were demonstrated between LEF and MTX or between LEF and SSZ.
Inhibition of structural damage

- Sharp, JT. Scoring Radiographic Abnormalities in Rheumatoid Arthritis, Radiologic Clinics of North America, 1996; vol. 34, pp. 233 to 241
LEF was statistically significantly superior to placebo in inhibiting the progression of disease by the Sharp Score.

No consistent differences were demonstrated between LEF and MTX or between LEF and SSZ.
Improvement in physical function

Change in Functional Ability Measure

<table>
<thead>
<tr>
<th>Trial</th>
<th>Change in Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>US301 (12 months)</td>
<td>L = -0.45, M = -0.03, P = -0.26</td>
</tr>
<tr>
<td>MN301 (6 months)</td>
<td>L = -0.56, S = -0.57, P = -0.08</td>
</tr>
<tr>
<td>MN302 (12 months)</td>
<td>L = -0.44, M = -0.54</td>
</tr>
</tbody>
</table>

*as measured by HAQ Disability Index
L = Leflunomide, M = Methotrexate, P = Placebo, S = Sulfasalazine
The combination of LEF and MTX was effective and well tolerated in the treatment of active RA patients.

This combination may be a useful option as an initial treatment for active RA before starting biological agents.
## Biologic DMARDs:

<table>
<thead>
<tr>
<th>Anti-TNF</th>
<th>Non TNF</th>
</tr>
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<tbody>
<tr>
<td>Etanercept</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Anakinra</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Abatacept</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>Tocilizumab</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Tofacitinib</td>
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</table>

### Non TNF
- Rituximab
- Anakinra
- Abatacept
- Tocilizumab
- Tofacitinib
Consensus statements do not recommend their use until at least one nonbiologic DMARD, usually MTX, has been administered without sufficient success

Severe adverse events
- generation of antibodies against these compounds
- emergence of antinuclear antibodies (ANAs)
- drug-induced lupus-like syndromes, and
- infections (including tuberculosis)

Immunogenicity has been shown to occur in adalimumab and infliximab reducing their efficacy
<table>
<thead>
<tr>
<th><strong>Anti-TNF-α</strong></th>
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</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>50 mg every wk SC</td>
</tr>
<tr>
<td>Infliximab</td>
<td>3 mg/kg every 8 wks IV</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>40 mg every 2 wks SC</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>200 mg every 2 wks SC</td>
</tr>
<tr>
<td>Golimumab</td>
<td>50 mg every 4 wks SC</td>
</tr>
<tr>
<td></td>
<td>Decoy receptor for TNF-α</td>
</tr>
<tr>
<td></td>
<td>Antibodies to TNF. Infliximab must be given in combination with methotrexate</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th><strong>Anti-B-cell therapy</strong></th>
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<tbody>
<tr>
<td>Rituximab</td>
<td>1000 mg IV; repeat after 2 wks</td>
</tr>
<tr>
<td></td>
<td>Pre-medication with methylprednisolone 100 mg IV, chlorphenamine 10 mg IV and paracetamol given 30 min prior to each infusion</td>
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<table>
<thead>
<tr>
<th><strong>Inhibitor of T-cell activation</strong></th>
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<tbody>
<tr>
<td>Abatacept</td>
<td>125 mg SC once a week</td>
</tr>
<tr>
<td></td>
<td>Favourable safety profile</td>
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<thead>
<tr>
<th><strong>Anti-IL6</strong></th>
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<tbody>
<tr>
<td>Tocilizumab</td>
<td>8 mg/kg every 4 wks IV</td>
</tr>
<tr>
<td></td>
<td>More effective than anti-TNF in methotrexate-intolerant patients</td>
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</tbody>
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<table>
<thead>
<tr>
<th><strong>Anti IL-1</strong></th>
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<tbody>
<tr>
<td>Anakinra</td>
<td>100 mg daily, SC</td>
</tr>
<tr>
<td></td>
<td>Less effective than other biological drugs</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
</tr>
<tr>
<td>------------------------------</td>
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<tr>
<td>ADA Heimans 2013 (IMPROVED)</td>
<td>2013</td>
</tr>
<tr>
<td>Horslev-Petersen 2013 (OPERA)</td>
<td>2013</td>
</tr>
<tr>
<td>van Eijk 2012 (STREAM)</td>
<td>2012</td>
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</tbody>
</table>
Tofacitinib

- **Oral Biologic RA Treatment**
- Approved in November of 2012
- New class of drugs called Janus Kinase (JAK) inhibitors
- For moderate-to-severe RA who have had an inadequate response to methotrexate.
- Can be used alone or with nonbiologic DMARDs such as methotrexate
- Side effects such as infections, cancer, and stomach or intestinal tears.
Efficacy of Tofacitinib on ACR20 response criteria at 24 weeks
Biological DMARD±conventional synthetic DMARD versus conventional synthetic DMARD
Biological DMARD+MTX combination versus conventional synthetic DMARD

**HIT HARD study**
- ADA+MTX more effective than moderate dose MTX

**IMAGE study**
- bDMARD+MTX were superior to placebo+MTX in MTX-naive RA (RR (95% CI) 1.68 (1.54 to 1.84) for ACR 70 responses)
- bDMARD+MTX were superior to placebo+MTX in MTX-IR (RR (95% CI) 4.07 (3.21 to 5.17))
- bDMARD+csDMARD more effective than csDMARD in mixed DMARD –IR (RR (95% CI) 4.74 (2.63 to 8.56)
Biological DMARD monotherapy versus conventional synthetic DMARD

FUNCTION study – Efficacy and safety of TCZ 8 mg/kg monotherapy vs MTX monotherapy

- TCZ 8 mg/kg monotherapy group met its primary endpoint (DAS28 ESR remission at 6 months) 38.7% vs 15% in MTX monotherapy group, respectively, p≤0.0001
- Radiographic progression at 12 months was lower in those receiving TCZ than MTX, and lowest in the TCZ 8 mg/kg+MTX combination group.
Biological DMARD+MTX combination versus biological DMARD monotherapy

Open-label JESMR study

- ETN+MTX was superior to ETN monotherapy for clinical outcomes

SURPRISE study and ACT-RAY study

- TCZ with MTX (combination) with switching from MTX to TCZ monotherapy (MTX-withdrawal).
  - Similar ACR 70 responses were seen for both groups at 6months

- 12-month data from the ACT-RAY study showed
  - higher proportions of DAS28 remission (DAS28 remission37% vs 46%, \( p=0.03 \)) and
  - radiographic non-progression (86% vs 92%, \( p=0.007 \)) in the TCZ monotherapy and TCZ +MTX groups, respectively)
Head-to-head biological DMARD studies

- The ADACTA study evaluated bDMARD monotherapy, comparing TCZ versus ADA.

- Significantly greater change in DAS28 from baseline to 6 months in the TCZ 8 mg/kg monotherapy versus ADA 40mg SC monotherapy group (95% CI): −1.5 (−1.8 to −1.1), p<0.0001).
Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis

TAKE HOME MESSAGES

- Drug selection should be based on
  - Early vs established disease
  - Presence or absence of poor prognostic factors
  - Efficacy
  - Adverse events and
  - Cost-benefit and
  - Evidenced based trials

- MTX remains in the corner stone in the treatment of RA
- Biologic DMARDs can be used when situation permits.
- Combination treatment of MTX with other DMARDs showed better efficacy
Thank You