Is Methotrexate A Disease Modifying Agent In Psoriatic Arthritis?

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Key Publications

1. NOR-DMARD Registry

2. MIPA Trial

3. RESPOND Trial

Summary

- Existing Guidance
- Historic Data
- New Data
  - NOR-DMARD registry
  - MIPA Trial
  - RESPOND Trial

Psoriasis/Psoriatic Arthritis Guideline
SIGN: Scottish Intercollegiate Guidelines Network 2010

- Dermatology/rheumatology teams
  - Should work closely together
- Use methotrexate to treat psoriatic arthritis
  - Especially when severe cutaneous psoriasis
- For peripheral psoriatic arthritis
  - Use leflunomide or sulfasalazine as alternatives
- Treat with biologics
  - Active psoriatic arthritis
  - Failed to respond/intolerant/contra-indications to 2 DMARDs
Guidelines all recommend methotrexate which implies strong evidence base

But reality is different which is shown in rest of talk

Exploring the Evidence for DMARDs in Psoriatic Arthritis

- Aim of DMARD therapy is to improve outcome not just symptoms
- Improvement in disease outcome best predicted by
  - disease activity scores (particularly swollen joint and acute phase response elements)
  - function (HAQ)
  - imaging?
- Definitive demonstration of DMARD activity is hard to confirm outside placebo-controlled RCTs

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Sulfasalazine For Psoriatic Arthritis

221 patients, 2gm Sulfasalazine, 36 weeks treatment

Results are on borderline for statistical significance
Leflunomide For Psoriatic Arthritis
190 patients, 20mg Leflunomide, 24 weeks treatment

Results are of strong statistical and clinical significance

Kaltwasser et al, Arthritis Rheum, 2004

Methotrexate For PsA
Historic Placebo-Controlled RCTs

IV Methotrexate (Black et al, 1964)
- 3 IV Pulses of MTX/placebo in 21 patients with PsA
- MTX improved joint counts and ESR
- But one death (marrow aplasia) and many side effects
- Too toxic for routine use

Oral Methotrexate (Willkens et al, 1984)
- 3 months RCT of oral MTX (7.5-15mg weekly)/placebo in active PsA
- MTX improved physicians global assessment
- No effect on joint counts/ESR

Other RCTs Of Methotrexate For PsA

Immediate vs Delayed MTX (Scarpa et al., 2008)
- 6 month RCT of 35 patients with early PsA
- All clinical variables improved
- Swollen joint counts improved more rapidly with early MTX

Methotrexate with ciclosporin (Spadaro et al., 1995)
- 12 month RCT of 35 patients with active PsA
- Similar improvements with both

Adding Ciclosporin/Placebo to MTX (Fraser et al, 2005)
- 12 month RCT 72 patients with active PsA
- Both groups improved over time
- Only significant treatment effect was on PASI scores

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NOR-DMARD: Routine Practice Registry
Observational Comparison of PsA with RA

• Longitudinal observational multicentre study
• Based in Norway
• MTX naive patients
  – 430 with PsA
  – 1218 with RA
• 6 month clinical and laboratory outcomes

NOR-DMARD Register
MTX Has Apparently Similar Effect in PsA and RA

Baseline Values

Changes At 6 Months

Lie et al, Ann Rheum Dis, 2010
Synopsis of NOR-DMARD Findings
Effectiveness and retention rates of MTX in PsA compared to RA

- After 6 months MTX
  - PsA and RA patients show improvements in most disease activity measures and patient reported outcomes
  - In adjusted analysis less improvement with PsA, but changes in same range as RA
  - EULAR good/moderate responses were achieved by 24%/57% PsA and 33%/70% RA

- At 2 years
  - Retention rates on methotrexate were 65% PsA and 66% RA
  - Only minor differences in reasons for discontinuation

Hypothesis: Methotrexate improves disease activity and function in psoriatic arthritis
Design: 6-month RCT comparing methotrexate with placebo

Inclusion
- Synovitis in ≥ 1 joint
- Psoriasis skin/nails

Exclusion
- Other arthropathies
- Recent steroids/DMARDs
- Contra-indications to MTX

Intervention
- Methotrexate (target 15mg/wk)
- Matching placebo

Primary outcome
- Psoriatic Arthritis Response Criteria

Secondary outcomes
- Patient Global Assessments
- Assessor Global Assessments
- HAQ & Pain
- Tender & Swollen Joint Counts
- ESR & CRP
- Composite Measures (ACR20)

Composite Measures
Formal Statistical Analysis Using Logistic Regression
Multiple Imputation, Adjusted For Age, Gender and Disease Duration

Changes in Composite Measures Over 6 Months
Completer Analysis With All Observed Data
Poor responders withdraw and effect may be over-estimated
Composite Measures
Completer Analysis with Observed Data

3 Months
6 Months

Individual Measures
Over 6 Months

Intention to Treat Analysis With All Observed Data
May over-estimate benefits but allows exploration of individual outcomes

Global Assessments And Pain

Joint Counts, ESR and HAQ

Effect of Methotrexate on Individual Outcomes in the MIPA Trial

Impact Of Pattern Of PsA Arthritis
Oligoarthritis, Polyarthitis & RA Like Show No Statistically Significant MTX Effects

Effect measure | Effect in MIPA
---|---
Tender joint count | No
Swollen joint count | No
ESR | No
C-reactive Protein | No
HAQ | No
Pain | No
Patient global | Yes
Physician's global | Yes

Disease Modifying | Symptom Modifying
Composite Measures
Comparisons With Other Treatments In PsA and RA

PsARC
- 2.7
- 3.0
- 1.7
- 1.8

ACR20
- 2.3
- 2.1

MIPA Results With Methotrexate
Replicate Routine Practice in 430 Patients

430 Norwegian PsA Patients in NOR-DMARD Observational Study Of Methotrexate
Lie et al, Ann Rheum Dis, 2010

Key Findings In MIPA
MTX In PsA
- Improves symptoms
- Has no effect on joint counts or acute phase response
- It is a “symptom modifying agent” and not a “DMARD”

MIPA Data Reliable
- Substantial data
- Equal largest placebo-controlled PsA trial
- Replicates findings in routine practice

MIPA Trial Limitations
- Trial Design Issues
  - Not long/large enough
- Patient Subtype
  - Not powered to study specific PsA subtypes
- Dose
  - 20-25mg may be needed
- Combination Treatment
  - TICOPA trial (currently recruiting in UK)
  - RESPOND trial

RESPOND Trial
- Open-label study
- Patients with active PsA
  - MTX naive/no DMARDs
- Randomly assigned
  - Infliximab (5 mg/kg) plus MTX (15 mg/week)
  - MTX (15 mg/week) alone
- ACR Response Rates
  - 2, 6, 12 and 14 weeks

ACR Responses In RESPOND
All patients taking methotrexate

ACR 20 Responders

ACR 50 Responders

Minimal Disease Activity In RESPOND

Infliximab/MTX vs MTX Alone

Baranauskaite et al, Ann Rheum Dis, 2011
**Synopsis Of RESPOND Trial**

- **Significant limitations**
  - Small sample size (243 planned, 115 recruited, 94 completed)
  - Open label design without placebo group
- **Shows infliximab is effective in PsA**
  - Larger changes than in IMPACT trials (previous infliximab RCTs) perhaps because patients had early disease
- **Suggests patients may improve with MTX alone**
  - High ACR20 responses in MTX-alone group "support ... recommendations to use MTX in active psoriatic arthritis"
  - Definitive conclusions cannot be drawn about MTX alone or in combination because of study design
- **More adverse effects with combination therapy**

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**Etanercept For Psoriatic Arthritis**

60 patients, 25mg Etanercept twice weekly, 12 weeks treatment

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<tr>
<th>PsARC Responder</th>
<th>ACR20 Responder</th>
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<tr>
<td>Etanercept</td>
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Results are of very strong statistical and clinical significance

Mease et al, Lancet, 2000

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**Acknowledgements for MIPA**

We would like to acknowledge the help of the Kings Clinical Trials Unit, the support of our funders and the contribution of patients and staff at all the MIPA trial centres

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**Treating Active Psoriatic Arthritis**

**Value to Patients With Active Disease**

- **Symptomatic Effects**
  - Methotrexate
  - Sulfasalazine
  - NSAIDs
- **Uncertain Effects**
  - Ciclosporin
  - Hydroxychloroquine
  - Non-TNF biologics
- **Disease Modifying**
  - Leflunomide
  - TNF inhibitors

**Implications for Clinical Practice**

- MTX (15mg weekly) not optimal for active PsA joints as not DMARD
  - Effective at higher doses or in combination regimes but RCTs needed
- Guidelines for the treatment of psoriatic arthritis need reconsidering
  - What should be recommended as a first choice DMARD?
  - Should biologics be used as initial or early treatment in active PsA?
  - Individualised regimes, recognising all aspects of PsA, may be needed