Pros and cons of MTX in combination with biologics vs. monotherapy in axSpA and PsA

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Pros & Cons of Use of MTX (± biologics) in SpA & PsA

- Does MTX on its own have any efficacy in PsO, PsA & spondyloarthritis?
- Is combination therapy of MTX + biologics better in improving outcomes in PsA & SpA than biologics alone?
- Does addition of MTX to biologics lead to reduction of anti-drug-antibody formation and improve biologic survival?
- What is the current practice?
- What should we be doing?
An Intensified Dosing of SC MTX in Plaque Psoriasis (METOP): A 52-Wk, Phase 3 RCT

• Evaluate the effect of intensified dosing of S/C MTX on moderate to severe plaque psoriasis, DBRPC 52 week study, n=120

• Patients randomized to S/C MTX 17.5 mg weekly (n=91) vs placebo (n=29)
  – At week 8, dose escalation to 22.5 mg if PASI50 not achieved, at week 16, all patients receive MTX (Folic acid 5 mg/week)

• Results
  – PASI75 at week 16: 41% vs 10% in MTX vs PBO group
  – Generally well tolerated

• Conclusion: MTX can be started at higher dose

METOP Trial

MIPA Trial: Is MTX a DMARD in PsA?

- Double-blind, parallel-group randomized controlled trial (N = 221)
- Patients randomized to receive MTX (target dose 15 mg/week) or PBO

<table>
<thead>
<tr>
<th>Global Index</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>PsARC (primary endpoint)</td>
<td>1.77 (0.97, 3.23)</td>
<td>0.06</td>
</tr>
<tr>
<td>ACR 20 responders</td>
<td>2.00 (0.65, 6.22)</td>
<td>0.23</td>
</tr>
<tr>
<td>DAS28 responders</td>
<td>1.70 (0.90, 3.17)</td>
<td>0.10</td>
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</table>

- There was no difference between groups in CRP/ESR, SJC, or TJC at 3 or 6 months
- There were significant differences in improvement in patient and physician global assessment and PASI scores ($P = 0.02, 0.01, \text{ and } 0.02, \text{ respectively}$)
- There was no evidence MTX improves inflammatory synovitis in active PsA

Limitations of MIPA Trial

• All outcomes favored MTX
  – But only patient and physician global estimates met the P<.05 criterion

• Results probably explained by
  – Insufficient statistical power
  – Wide individual variation
  – No evaluation of subsets
  – Low doses

• MTX appears less efficacious in PsA than RA

Effectiveness of MTX in PsA at wk16: Open-Label Trial

PsA pts treated with IFX (5mg/kg) + MTX (n=57) or MTX alone (n=58) in an open-label trial. All patients were MTX naïve

TICOPA Trial: Experience with MTX

- Tight control: MTX monotherapy X 12 wks, then Rx adjusted to reach MDA (48 wks)
- Standard-care: mostly MTX throughout study
- 188 patients took oral MTX 12 weeks
- MTX dose: 175 ≥5 mg; 122 ≥20 mg; 86 to 25 mg
- At 12 weeks
  - ACR20: 41%
  - MDA achieved by 22%
  - Dactylitis improvement: 62%
  - Enthesitis improvement: 25%
  - Minimal benefit in nails

Does MTX improve outcomes if added to Biologics in PsA patients?

- To investigate this, we need a trial of PsA patients who are MTX naïve, and randomize them to receive either MTX alone, biologic alone, or biologic plus MTX.
- Such a trial doesn’t exist (but is currently being conducted with etanercept).
- All available clinical trials on biologics in PsA (TNFi, IL12/23i, IL-17i) are done on patients taking or not taking baseline MTX.
- These trials have not shown better efficacy of biologics in patients on baseline MTX treatment.
IMPACT 2 Trial: Improvement in Joint and Skin With or Without Baseline Methotrexate Usage

ACR 20 at Week 14

PASI 75 at Week 14

# Bottom-line on MTX Efficacy in PsO/PsA

<table>
<thead>
<tr>
<th>MTX Use in Randomized Trials</th>
<th>Does it work?</th>
<th>Editorial comments</th>
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<tbody>
<tr>
<td>METOP (PsO) 2017</td>
<td>YES</td>
<td>MTX really works for psoriasis!</td>
</tr>
<tr>
<td>MIPA (PsA) 2012</td>
<td>NO</td>
<td>The only DBRPCT, but heavily criticized</td>
</tr>
<tr>
<td>RESPOND (PsA) 2012</td>
<td>Yes</td>
<td>Open Label, no placebo control</td>
</tr>
<tr>
<td>TICOPA (PsA)</td>
<td>Yes</td>
<td>Open Label, no placebo control</td>
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<tr>
<td>Pivotal trials on TNFi, IL-12/23i, IL-17i</td>
<td>We don’t know</td>
<td>These are not designed to answer the question “is combo Rx of MTX + Biologic better than solo biologic”</td>
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</table>
(Old) GRAPPA PsA Treatment Guidelines

Peripheral Arthritis
- NSAIDs, IA steroids, DMARDs (MTX, CsA, SSZ, LEF), Biologics (anti-TNF)

Skin and Nail Disease
- Topicals
- PUVA/UVB
- DMARDs (MTX, CsA)
- Biologics

Axial Disease
- NSAID
- PT
- Biologics (anti-TNF)

Dactylitis
- NSAID
- Injection
- Biologics (anti-TNF)

Enthesitis
- NSAID
- Injection
- Biologics (anti-TNF)

Reassess Response to Therapy and Toxicity

(New) GRAPPA PsA Tx recommendations 2016

Which domains are involved?

Peripheral arthritis
- DMARDs (MTX, SSZ, LFN), TNFi or PDE4i
- Biologics (TNFi, IL12/23i, IL17i) or PDE4i
- Switch biologic (TNFi, IL12/23i or IL17i)

Axial disease
- NSAIDs only
- TNFi, IL17i or *IL12/23i
- Switch biologic (TNFi, IL12/23i or IL17i)

Enthesitis
- NSAIDs
- Biologics (TNFi, IL12/23i, IL17i) or PDE4i
- Switch biologic (TNFi, IL12/23i or IL17i)

Dactylitis
- NSAIDs
- DMARDs (MTX, LEF, SSZ) or PDE4i
- Switch biologic (TNFi, IL12/23i, IL17i) or PDE4i

Skin
- Topicals (keratolytics, steroids, vit. D analogues, emollients, calcineurin i)
- Phototx or DMARDs (CSA, LEF, MTX, acitretin)

Nails
- Biologics (TNFi, IL12/23i, IL17i) or PDE4i
- Topical or procedural or DMARDs (CSA, LEF, MTX, acitretin)

No direct evidence for therapies in axial PsA recommendations based on axial SpA literature

CS injections: consider on an individual basis due to potential for serious side effects; no clear evidence for efficacy

Assess activity, impact and prognostic factors

Standard therapeutic route

Expedited therapeutic route

S/C Methotrexate Trial in AS

- Open-label clinical trial on 20 AS patients with BASDAI >4 (mean 5.6)
- MTX 15 mg S/C for 4 weeks, then 20 mg S/C for next 12 weeks
- BASDAI scores, physical function, spinal mobility, patients' & physicians' global assessment, peripheral joint counts, SF36 and CRP assessed
- 1st outcome: ASAS20 at week 16
- Results: 20% (5/20) had ASAS20
- No significant improvement in any other clinical parameter or CRP

2013 Cochrane Review of MTX in AS

- They identified three RCTs, with 116 participants
- They included outcomes of response, physical function, pain, spinal mobility, peripheral joints/entheses pain, swelling, tenderness, changes in spine radiographs, and patient and physician global assessment
- **AUTHORS' CONCLUSIONS**: There is not enough evidence to support any benefit of MTX in the treatment of AS. High-quality RCTs of larger sample sizes are needed to clarify the effect(s) of MTX on AS

Recommendations for the treatment of active AS

**NSAIDs**
- Use continuously
- No preferred drug

**Physical Therapy**
- Active over passive
- Land-based over aquatic

**Systemic glucocorticoid**
- Consider if peripheral flare, pregnancy, IBD flare

**Slow-Acting Drugs** (SSZ, pamidronate)
- Consider if peripheral arthritis or TNFi contraindications

**TNFi contraindication**
- Remains active

**Non-TNFi biologic**
- Use infliximab or adalimumab
- Use TNFi monoclonals

**Remains active**
- Recurrent iritis

**Alternative TNFi**
- Isolated sacroiliitis
  - Local GC
- Peripheral arthritis
  - Local GC
  - Consider if ≤ joints; use infrequently
- Enthesitis
  - Local GC
  - Avoid achilles, patellar, quadriceps

**LEGEND**
- Strongly recommend
- Conditionally recommend
- Conditionally recommend against
- Strongly recommend against
- Qualifier

Monitor validated AS disease activity measure, and CRP or ESR regularly

Unsupervised back exercises, formal group or individual self-management education, fall evaluation/counseling

Why would MTX work in *peripheral joints* in RA, but not in *axial joints* of spondyloarthritis?

**Synovitis is the predominant pathology in the peripheral joints in RA**

**Osteitis & Enthesitis is the predominant pathology in the axial joints of SpA**

MTX works on Synovitis, but not on enthesitis and osteitis

Reference: Deodhar A. 2017 NWRS Meeting: *Pure Speculation!*
Anti-drug antibodies are implicated in:
- Increased infusion reactions
- Lower drug levels
- Blunted clinical response

- Non-neutralizing ADAs are against allotope – portion of drug not essential for activity
- Neutralizing ADAs are against idiotopes – portion of drug essential for activity
Influence of methotrexate on infliximab pharmacokinetics & pharmacodynamics in AS

- IFX pharmacokinetics studied in a DBRT of 18 weeks: IFX (mono RX) vs IFX + MTX on 26 patients with AS
- “A two-compartment model with first-order distribution & elimination constants” used
- 507 blood samples & 329 BASDAI measurements collected
- “Contrary to what is observed in RA, MTX influences neither infliximab pharmacokinetics nor concentration–response relationship in AS”
- MTX did not influence BASDAI response in IFX treated patients

Effect of co-medication with csDMARD on drug retention & clinical effectiveness of TNFi Rx in axSpA

- All axSpA pts starting TNFi Rx in Swiss Clinical Quality Management cohort
- Crude drug retention analyzed using Kaplan-Meier plots, Cox proportional hazards regression used in adjusted analyses to model TNFi discontinuation
- 1,914 patients, 2,765 TNFi Rx courses, 20.4% combo with csDMARDs
- In multivariate adjusted analyses, the mono Rx group had significantly lower TNFi retention, HR 1.17 (95% CI 1.01–1.35), the effect was larger for IFX treated patients, HR for monotherapy 1.36 (95% CI 1.06–1.74)

Combination of a TNFi with csDMARDs has improved drug retention

Effect of co-medication with csDMARD on drug retention of TNFi Rx in axSpA

- Previous observational studies do not account for “confounding by indication”
- SpA pts (n=954) from Rheumatic Diseases Portuguese Register starting TNFi between 2001-14, 41% treated with csDMARD
- 1\textsuperscript{0} outcome: time to 1st TNFi discontinuation
- Cox-regression used to estimate effect of csDMARD co-medication on TNFi-retention
- **Conclusion**: co-medication with csDMARDs had no effect on TNFi-retention

30% discontinue TNFi in 2.5 yrs
56% for inefficacy, 31% for SE

PS= Propensity score matching

Two studies with opposite outcomes!
Which one to believe?

Portuguese Study

Swiss Study

HR = 1.17, p = 0.03

YEAR | 0  | 1  | 2  | 3  | 4  | 5  |
-----|----|----|----|----|----|----|
Comb | 565| 401| 306| 246| 192| 160|
Mono | 2200| 1332| 994| 754| 564| 435|
# Bottom-line on MTX Efficacy in axSpA

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<th>Does it work?</th>
<th>Editorial comments</th>
</tr>
</thead>
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<tr>
<td>Haibel (AS) 2007</td>
<td>NO</td>
<td>S/C MTX did not work at week 16</td>
</tr>
<tr>
<td>Cochrane Review (AS) 2013</td>
<td>NO</td>
<td>Only 3 RCT found!</td>
</tr>
<tr>
<td>Nissen (MTX added to IFX) 2016</td>
<td>Yes</td>
<td>30% Swiss patients remain on the TNFi after 5 years. Believable.</td>
</tr>
<tr>
<td>Sepriano (MTX added to IFX) 2016</td>
<td>NO</td>
<td>50% Portuguese patients stay on the same TNFi after 8 years! Really?</td>
</tr>
<tr>
<td>Pivotal trials on TNFi, IL-17i</td>
<td>We don’t know</td>
<td>These are not designed to answer the question “is combo Rx of MTX + Biologic better than solo biologic”</td>
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What is the current practice? Are people using MTX in the treatment of axial spondyloarthritis?
Rates of DMARD use among rheumatologists for management of AS & nr-axSpA: MAXIMA Study

- Online survey of rheumatologists (56 countries, n=809)
- Questions re referral pattern, diagnosis & management of AS & nr-axSpA
- In western Europe & in north America (US & Canada), 70-80% of academic rheumatologists use MTX in the management of axSpA

## Use of MTX in the Rx of AS in Latin America

<table>
<thead>
<tr>
<th></th>
<th>Argentina</th>
<th>Chile</th>
<th>Spain</th>
<th>Mexico</th>
<th>Peru</th>
<th>Portugal</th>
<th>Uruguay</th>
<th>Venezuela</th>
<th>Costa Rica</th>
<th>Total Iberian countries</th>
<th>BRASIL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs (%)</strong></td>
<td>77.5%</td>
<td>83.4%</td>
<td>73.0%</td>
<td>94.0%</td>
<td>0.0%</td>
<td>94.8%</td>
<td>98.0%</td>
<td>97.1%</td>
<td>97.0%</td>
<td>71.2%</td>
<td>77.0%</td>
</tr>
<tr>
<td><strong>CS (%)</strong></td>
<td>29.0%</td>
<td>40.3%</td>
<td>15.0%</td>
<td>11.0%</td>
<td>15.3%</td>
<td>29.0%</td>
<td>9.0%</td>
<td>46.4%</td>
<td>39.4%</td>
<td>18.5%</td>
<td>7.5%</td>
</tr>
<tr>
<td><strong>SSZ (%)</strong></td>
<td>12.0%</td>
<td>27.5%</td>
<td>15.0%</td>
<td>35.0%</td>
<td>56.7%</td>
<td>47.3%</td>
<td>28.0%</td>
<td>40.6%</td>
<td>45.5%</td>
<td>18.8%</td>
<td>21.3%</td>
</tr>
<tr>
<td><strong>MTX (%)</strong></td>
<td><strong>49.0%</strong></td>
<td>44.0%</td>
<td>17.0%</td>
<td>30.0%</td>
<td>23.3%</td>
<td>23.1%</td>
<td>36.0%</td>
<td><strong>53.6%</strong></td>
<td><strong>33.3%</strong></td>
<td><strong>23.9%</strong></td>
<td><strong>26.2%</strong></td>
</tr>
<tr>
<td>Biological agents (%)</td>
<td>10.4%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>12.1%</td>
<td>1.7%</td>
<td>10.8%</td>
<td>0.0%</td>
<td>27.0%</td>
<td>12.1%</td>
<td>2.9%</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

*NSAIDs = non-steroidal anti-inflammatory drugs; CS = corticosteroids; SSZ = sulphasalazine; MTX = methotrexate.*
In Summary

- Methotrexate on its own, has **very good efficacy** in psoriasis, **some efficacy** in PsA, and **no efficacy** in axial spondyloarthritis (axial joints).
- It is not known whether MTX adds any efficacy if combined with a biologic agent either in PsA or axSpA.
- There are conflicting results on whether MTX improves TNFi drug survival in axSpA.
- Recommendations after review of literature:
  - Use MTX in PsO & PsA, but closely monitor clinical efficacy. If no or minimal response in 12 weeks, change to another agent.
  - Do Not use MTX in axSpA for axial disease.
  - Use of MTX for peripheral arthritis, or to improve TNFi survival in axSpA is controversial and I do not use it.