Defining Remission in Rheumatoid Arthritis
Part 1:

Why is a new remission definition in rheumatoid arthritis needed?
Background

- Increasing numbers of patients reach remission
- Abundance of remission definitions
  - ‘strict’ definitions: American Rheumatism Association (Pinals); SDAI/CDAI
  - ‘loose’ definitions: DAS/DAS28; mARA; SJC0/TJC0/ESR10; MDA

→ Need for a uniform definition
   (RA trials, practice)
Etymology

- *Remittere* (L): to send back; to decrease; to relax...
- *Remission*
  - (med dictionary): an abatement or lessening of the manifestations of a disease
  - (Wiki): the state of absence of disease activity in patients with a chronic illness, with the possibility of return of disease activity
Concept: Key Points

• Remission is a state, not change or transition

• Absence of disease activity
Concept: Remission

- Related but not identical to remission:
  - *Cure*: disease does not return
  - *Arrest*: disease progression is stopped
  - *Intermission*: period of no activity between two periods of active disease

- Remission is antithetical to the following:
  - *Relapse*: return of disease activity
  - *Flare*: substantial increase of disease activity
Current Definitions: American Rheumatism Association*

- 5 or more must be fulfilled for at least 2 consecutive months:
  - Morning stiffness not exceeding 15 minutes
  - No fatigue
  - No joint pain (by history)
  - No joint tenderness or pain on motion
  - No soft tissue swelling in joints or tendon sheaths
  - ESR (W) < 30 mm/h (f); < 20 mm/h (m)

ARA (Pinals)

• 3 groups of RA patients classified according to the rheumatologist:
  – complete remission
  – partial remission
  – active disease

• Sensitivity 72%;
  Specificity 90% (against partial remission)
Problems with ARA (Pinals) Definition

• Depends on measures not widely assessed now in RA trials:
  – Morning stiffness
    (absent in many patients with active RA)
  – Tendon sheath swelling

• Very strict definition
  – Attainment very rare in RA trials
  – Thus unrealistic target for treatment success

• Many unvalidated modifications in use
DAS/DAS 28
Threshold for Remission*

- DAS: Ritchie joint index and 44 swollen joint ct
- DAS28: 28 tender & swollen joint count
- ESR/CRP versions
- Both use a ‘general health’ VAS (0-100)

- DAS28 remission:  < 2.6
- DAS remission:  < 1.6

DAS/DAS28 Remission

• Validation against ARA (Pinals) criteria in Nijmegen data, moderately active disease
• Modified ARA (Pinals) criteria used:
  – Fatigue not assessed
  – Remission defined as 4 out of 5 remaining criteria
• Sensitivity and specificity against modified ARA (Pinals) 87%
SDAI/CDAI Remission

- SDAI = (28TJC) + (28SJC) + MDGA + PtGA + CRP*
- CDAI = (28TJC) + (28SJC) + MDGA + PtGA*
- SDAI remission \( \leq 3.3^{**} \)
- CDAI remission \( \leq 2.8^{**} \)

- Developed in patient profile exercise and validated in observational datasets

* Smolen JS et al. Rheumatology. 2003;42:244
Other Definitions of Remission and Related States

- PAS and RAPID3:* both based solely on patient reported outcomes
- Minimal Disease Activity:** developed at OMERACT, based on core set measures
- Yet other definitions exist, both for remission and minimal disease activity

Another Reason to Define Remission: Associated with Best Functional Outcome (BeSt Data)

Mean HAQ score at year 4

Mean disease activity at year 4

How Strict Are Current Definitions? Prevalence of Remission in QUEST-RA*

• Survey of RA patients in 24 countries

Levels of RA Disease Activity Measures Are Associated With X-ray Progression

Background: Conclusion

• ‘Strict’ and ‘loose’ definitions of RA remission
  – ARA (Pinals), CDAI/SDAI, PAS/RAPID3 - ‘strict’
  – Modified ARA, DAS28 - ‘loose’
• No definition universally used
• Variability in how each definition is operationalized
• Remission leads to better RA outcomes
• Agreement on need for uniform definition(s)
ACR/EULAR 2011 Provisional Definition of Rheumatoid Arthritis Remission:

How was it developed and how will it work?
Who was involved?

- A broad Parent Committee, including representatives of ACR, EULAR and OMERACT, set out goals, defined the tasks, evaluated interim analyses
  - RA trialists/clinicians + patient experts

- A smaller Working Committee carried out the analyses and presented findings to the Parent Committee
Outline of Approach

• Charge from committee
• Survey committee members on threshold for remission
• Address whether patient reported outcomes should be included
• Create possible definitions of remission
• Test possible definitions
  – Predictive validity
  – Face validity
• Decide on definition(s) of remission
• Address remaining concerns
Where did the data come from?

- Actual data from large, multicenter RA trials of 2nd line drugs/biologics
- Appreciation to:
  - Amgen, Abbott, Wyeth and others who shared data
- Industry had no role in criteria development process
ACR/EULAR Committee Requirements (1)

The definition should:

• be stringent
  – little, if any, residual active disease

• include at least the following core set measures
  – tender + swollen joint counts, acute phase reactant

• not include physical function
  – affected by disease duration
  – outcome used for validation

• not include presence or absence of treatment

• not include duration of remission
ACR/EULAR Committee Requirements (2)

The definition should further:

• predict good outcome  
  – later lack of x-ray damage and stable good function  

• be defined for trials  
  – subsequent modification for clinical practice  

• pass the OMERACT Filter*  
  – Truth: unbiased and relevant  
  – Discrimination: discriminate between relevant states  
  – Feasibility: easy to apply and to interpret

Core Set for RA Clinical Trials*

- Patient global assessment of disease activity
- Physician/Assessor global assessment of disease activity
- Pain
- Tender joint count (TJC)
- Swollen joint count (SJC)
- Physical disability
- Acute phase reactant

*Felson et al, Arthritis Rheum 1993;36:729-40;
Step 1: What cut points of core set measures are compatible with remission?

- Survey of 27 Committee members, including patients
- Asked to choose threshold for remission...
  - If a variable was the only measure used
  - If all other measures pointed to remission

→ RESULTS: thresholds for remission for most core set measures cluster around values of 1
What would be the threshold for remission if _______ was the only measure used?

<table>
<thead>
<tr>
<th></th>
<th>Mean (s.d.)</th>
<th>Median</th>
<th>80th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>TJC28</td>
<td>1.1 (1.3)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>SJC28</td>
<td>0.5 (0.9)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.9 (0.4)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pain (0-10 scale)</td>
<td>1.3 (0.7)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Physician Global Assessment (0-10)</td>
<td>1.0 (0.9)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Patient Global Assessment (0-10)</td>
<td>1.2 (0.8)</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
What would be the threshold for remission if all other measures pointed to remission?

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (s.d.)</th>
<th>Median</th>
<th>80\textsuperscript{th} percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>TJC28</td>
<td>2.6 (2.0)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>SJC28</td>
<td>1.3 (1.3)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>1.1 (0.6)</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Pain (0-10 scale)</td>
<td>2.4 (1.3)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Physician Global Assessment (0-10)</td>
<td>1.6 (1.0)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Patient Global Assessment (0-10)</td>
<td>2.2 (1.3)</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Step 2: Should patient reported outcomes be included?

- **PRO’ s**: patient global; pain
- Analysis of 4 large multicenter trials of TNF inhibitors + MTX vs. MTX alone
- What outcomes best identified the efficacy of the biologic/MTX combination?
  - Whatever outcomes had the most stringent p value discriminating comb. vs. MTX were the best outcomes
  - If PRO’ s discriminate comb. vs. MTX, they detect effect of treatment as well/better than non-PRO’ s
How do PRO’s rank among 7 core set outcome measures? Analysis of 4 trials

<table>
<thead>
<tr>
<th>Trial #</th>
<th>Patient Global Assessment</th>
<th>Patient Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial #1</td>
<td>1st</td>
<td></td>
</tr>
<tr>
<td>Trial #2</td>
<td>4th</td>
<td></td>
</tr>
<tr>
<td>Trial #3</td>
<td></td>
<td>2nd</td>
</tr>
<tr>
<td>Trial #4</td>
<td>not in top 4</td>
<td></td>
</tr>
</tbody>
</table>

PRO’s help identify effective treatments. At least one should be included in the definition of remission.
Step 3: What candidate definitions of remission should be tested?

- **Boolean Definitions**
  - Depend on meeting a (low) level in each of a series of separate disease activity measures

- **Index Definitions: DAS28, SDAI**
  - An index is a formula combining several measures
  - Definitions depend on meeting a (low) level in the index
Tested Definitions: Boolean

- TJC28, SJC28, CRP* all ≤ 1
- TJC28, SJC28, CRP, PatientGA* (PtGA) all ≤1
- TJC28, SJC28, CRP, Pain all ≤1
- TJC28, SJC28, CRP, PhysicianGA (PhGA), PtGA all ≤1
- TJC28, SJC28, CRP, PhGA, Pain all ≤1
- TJC28, SJC28, CRP, PtGA, Pain all ≤1
- TJC28, SJC28, CRP, PhGA, PtGA, Pain all ≤1

*GA: 0-10 scale; CRP: mg/dl
Indexes Tested

- **DAS28**
  
  \[ \text{DAS28} = 0.56 \sqrt{TJC28} + 0.28 \sqrt{SJC28} + 0.36 \ln(CRP \times 10 + 1) + 0.014 \times \text{PtGA (0-100 scale)} + 0.96 \]
  
  - Levels tested: DAS28 < 2.6; DAS28 < 2.0

- **SDAI (Simplified Disease Activity Index)**
  
  \[ \text{SDAI} = TJC28 + SJC28 + \text{PtGA (0-10 scale)} + \text{PhGA (0-10)} + \text{CRP (mg/dL)} \]
  
  - Level tested: SDAI < 3.3
Step 4: Predicative Validity
Comparing the Candidate Definitions

• Does remission predict later good outcome?
• Remission at month 6 should predict good outcome for x-ray and HAQ between 12 and 24 months:
  – X-ray - good outcome: change $\leq 0$ in modSharp or Sharp-vdH score
  – Function - good outcome: change $\leq 0$ in HAQ and HAQ score $< 0.5$
<table>
<thead>
<tr>
<th></th>
<th>Percent in Remission with Good Outcome</th>
<th>Percent NOT in Remission with Good Outcome</th>
<th>Positive Likelihood Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TJC28, SJC28, CRP ≤ 1</td>
<td>69%</td>
<td>50%</td>
<td>2.0</td>
<td>0.01</td>
</tr>
<tr>
<td>+ PtGA ≤ 1</td>
<td>77%</td>
<td>51%</td>
<td>2.9</td>
<td>0.006</td>
</tr>
<tr>
<td>+ Pain ≤ 1</td>
<td>74%</td>
<td>51%</td>
<td>2.6</td>
<td>0.01</td>
</tr>
<tr>
<td>+ PhGA and PtGA ≤ 1</td>
<td>77%</td>
<td>51%</td>
<td>2.9</td>
<td>0.01</td>
</tr>
<tr>
<td>+ PhGA and Pain ≤ 1</td>
<td>77%</td>
<td>51%</td>
<td>2.9</td>
<td>0.01</td>
</tr>
<tr>
<td>+ PtGA and Pain ≤ 1</td>
<td>76%</td>
<td>51%</td>
<td>2.8</td>
<td>0.001</td>
</tr>
<tr>
<td>+ PhGA, PtGA and Pain ≤ 1</td>
<td>76%</td>
<td>51%</td>
<td>2.8</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Validity of Index Remission Definitions: Predicting a Good Outcome for X-ray

<table>
<thead>
<tr>
<th>Indexes</th>
<th>Percent in Remission with Good Outcome</th>
<th>Percent NOT in Remission with Good Outcome</th>
<th>Positive Likelihood Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TJC28, SJC28, CRP, PtGA ≤1</td>
<td>77%</td>
<td>51%</td>
<td>2.9</td>
<td>0.006</td>
</tr>
<tr>
<td>DAS28&lt;2.6</td>
<td>60%</td>
<td>59%</td>
<td>1.0</td>
<td>0.93</td>
</tr>
<tr>
<td>DAS28&lt;2.0</td>
<td>70%</td>
<td>59%</td>
<td>1.6</td>
<td>0.48</td>
</tr>
<tr>
<td>SDAI≤3.3</td>
<td>77%</td>
<td>50%</td>
<td>3.0</td>
<td>0.003</td>
</tr>
</tbody>
</table>
## Validity of Candidate Remission Definitions: Predicting a Good Outcome for Both X-ray and HAQ

<table>
<thead>
<tr>
<th></th>
<th>Percent in Remission with Good Outcome</th>
<th>Percent NOT in Remission with Good Outcome</th>
<th>Positive Likelihood Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TJC28, SJC28, CRP ≤ 1</td>
<td>46%</td>
<td>17%</td>
<td>3.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>+ PtGA ≤1</td>
<td>66%</td>
<td>17%</td>
<td>7.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>+ Pain ≤1</td>
<td>60%</td>
<td>17%</td>
<td>5.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>+ PhGA and PtGA ≤1</td>
<td>68%</td>
<td>17%</td>
<td>8.0</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>+ PhGA and Pain ≤1</td>
<td>64%</td>
<td>18%</td>
<td>6.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>+ PtGA and Pain ≤1</td>
<td>64%</td>
<td>17%</td>
<td>6.8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>+ PhGA, PtGA and Pain ≤1</td>
<td>67%</td>
<td>18%</td>
<td>7.5</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Indicators</td>
<td>Percent in Remission with Good Outcome</td>
<td>Percent NOT in Remission with Good Outcome</td>
<td>Positive Likelihood Ratio</td>
<td>P Value</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------------------------------------</td>
<td>------------------------------------------</td>
<td>---------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>TJC28, SJC28, CRP, PtGA ≤1</td>
<td>66%</td>
<td>17%</td>
<td>7.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>DAS28&lt;2.6</td>
<td>38%</td>
<td>18%</td>
<td>2.2</td>
<td>0.01</td>
</tr>
<tr>
<td>DAS28&lt;2.0</td>
<td>56%</td>
<td>20%</td>
<td>4.5</td>
<td>0.01</td>
</tr>
<tr>
<td>SDAI≤3.3</td>
<td>56%</td>
<td>17%</td>
<td>4.8</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
Predictive Validity Analyses

- **Boolean definitions** with SJC, TJC, CRP and patient reported outcome(s) have similar predictive validity

- **Indexes** did not perform the same:
  - DAS28 < 2.6 did not predict later good outcome as well as DAS < 2.0 or SDAI ≤ 3.3
  - DAS28 < 2.0 did not predict x-ray outcome well and was achieved rarely (<1/3 as often as other index thresholds)
  - Possible explanation: in DAS28, TJC is strongly weighted; TJC predicts X-ray less well than SJC
Step 5: Face Validity

If you meet the remission definition, do you always have a low tender joint count?

- TJC, SJC, ESR, PtGA ≤1
- DAS28 < 2.6
- DAS28 < 2.0
- SDAI ≤ 3.3

maximal score
- 90%

eular
Step 5: Face Validity
If you meet the remission definition, do you always have a low swollen joint count?
Summary of Face Validity Analyses

• **Boolean definitions** required low SJC and TJC by definition
  – not more than 1 of both possible

• **For Indexes:**
  – SDAI
    • Maximum of 2 active joints possible (same for CDAI)
      – CRP in SDAI to be set to 0.5 if lower
    • Maximum of 2 active joints seen in analyses
  – DAS28
    • SJC and TJC of 3-6 active joints were not rare
    • These are incompatible with remission
Step 6: Committee Decision on Definition

- Committee meeting October 2009
- Split into two groups to discuss data – Same consensus achieved in both groups: One Boolean definition, one index definition
- Select one of these as outcome in each trial
- Report both
ACR/EULAR 2011 Provisional Definitions of Remission for Clinical Trials

- **Boolean Based Definition**
  At any time point, a patient must satisfy all of the following:
  - Tender Joint Count $\leq 1$
  - Swollen Joint Count $\leq 1$
  - CRP $\leq 1 \text{ mg/dL}$
  - Patient Global Assessment $\leq 1$ (on a 0-10 scale)

- **Index Based Definition**
  At any time point, a patient must have SDAI $\leq 3.3$
Global Assessment: How to Word the Question

• The following wording and response categories should be used for global assessment:

  Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?

• Verbal anchors for the response are ‘very well’ and ‘very poor’
### Percentage Achieving Remission in Recent Trials by Definition

<table>
<thead>
<tr>
<th>Remission definition</th>
<th>DMARD monotherapy (n=380)</th>
<th>Biological monotherapy (n=520)</th>
<th>Combination Therapy (n=330)</th>
<th>Total (n=1230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TJC,SJC,CRP ≤ 1</td>
<td>9</td>
<td>7</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>+ PtGA ≤ 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ PtGA, pain ≤ 1</td>
<td>8</td>
<td>6</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>+ PtGA, PhGA ≤ 1</td>
<td>8</td>
<td>7</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>+ PhGA, pain ≤ 1</td>
<td>8</td>
<td>6</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>+ PtGA, PhGA,pain ≤ 1</td>
<td>7</td>
<td>6</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>DAS28 &lt;2.6</td>
<td>19</td>
<td>17</td>
<td>35</td>
<td>21</td>
</tr>
<tr>
<td>DAS28 &lt; 2.0</td>
<td>5</td>
<td>8</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>SDAI ≤ 3.3</td>
<td>10</td>
<td>8</td>
<td>26</td>
<td>14</td>
</tr>
</tbody>
</table>
Concern 1:
28 Joints Used to Define Remission vs. Full Joint Count

What if foot/ankle joints active? Should patient be in remission?
In Patients with 28 Joint Count ≤ 1

• <10% had active ankles/feet
• In these, PtGA was often high, thus:
  – would not meet criteria for remission anyway
• How many not in remission when full joint counts used (i.e., ‘false positive’ for remission)?
• Compare drop in % remission in 2 trials:
  – Trial 1: from 6% (28 jt count) → 4% (full jt count)
  – Trial 2: from 14% → 9%
  – Yet, similar % of good outcome in remission:
    • 80-90% in full jt count remission
    • 1-4% less when only in 28 jt count remission
Recommendation for Joint Counts

• The new ACR/EULAR criteria do not require inclusion of ankles and forefeet in the assessment of remission but recommend that these joints are also included in the examination.

• Investigators should always report which joints were examined.
Concern 2:
What value of ESR corresponds to CRP = 1?

- In men with RA, CRP value of 1mg/dl corresponds roughly to 20mm/hour*

- In women with RA, CRP value of 1mg/dl corresponds roughly to 30mm/hour*

Other Concerns: Elements for the future?

• Fatigue
  – Could not be studied because trial datasets contained no information on it
  – Part of the research agenda
Other Concerns: Elements for the future?

- Fatigue

- Imaging
  - Need a clinical definition of remission now
  - Imaging standards not yet developed
  - Given high rate of synovitis in clinically inactive RA joints, not clear that a ‘no synovitis’ threshold on imaging could be achievable at present
Conclusion for Defining Remission in Trials

• New Definition of Remission in RA
  – Stringent
  – Achievable
  – Should be major outcome for trials
  – Variants on these definitions may be utilized in practice settings
Assessing RA Remission in Practice

• Acute Phase Reactant often unavailable during patient visit
• Can we suggest a definition of remission without Acute Phase Reactant?
• All data sets used to derive remission definition were from trials, not practice
• Trials are different from practice
  — Trials include only selected patients
    • high disease activity, otherwise comparatively healthy
  — Long term follow-up in trials is selective
Validity of Definitions without ESR/CRP: Predicting a Good Outcome for Both X-ray and HAQ

<table>
<thead>
<tr>
<th>Definition</th>
<th>Percent in Remission with Good Outcome</th>
<th>Percent NOT in remission with Good Outcome</th>
<th>Positive Likelihood Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TJC28, SJC28, CRP + PtGA ≤1</td>
<td>66%</td>
<td>17%</td>
<td>7.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SDAI ≤3.3</td>
<td>56%</td>
<td>17%</td>
<td>4.8</td>
<td>&lt;.0001</td>
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</tbody>
</table>

DEFINITIONS WITHOUT ACUTE PHASE REACTANTS

<table>
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<tr>
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<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TJC28, SJC28, PtGA &lt; 1</td>
<td>66%</td>
<td>16%</td>
<td>7.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CDAI ≤2.8*</td>
<td>63%</td>
<td>16%</td>
<td>6.4</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

*CDAI = sum of (TJC, SJC, Patient Global (0-10), Physician Global (0-10))
Defining Remission in Practice

• Definitions without Acute Phase Reactants perform comparably to those with them and could be used in practice:
  – TJC, SJC, Patient Global all $\leq 1$
  – CDAI $\leq 2.8$

• Remission definitions for practice are best defined using data from practice settings
ACR-EULAR 2011
Definition of Remission

For clinical trials
• Boolean
  – SJC, TJS, PtGA, CRP all ≤1
• Index-based
  – SDAI ≤3.3

For clinical practice
• Boolean
  – SJC, TJC, PtGA all ≤1
• Index-based
  – CDAI ≤2.8

SDAI=SJC+TJC+PhGA+PtGA+ CRP (mg/dl)  CDAI=SJC+TJC+PhGA+PtGA
Conclusion about Defining Remission in Practice

• Remission predicts the best clinical, functional and structural outcomes

• ACR/EULAR definitions of remission were developed using trial data and need to be validated for use in practice settings
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