

Title: What should be the primary target of 'treat to target' in PsA?

Laura C Coates, Ennio Lubrano, Fabio Massimo Perrotta, Paul Emery, Philip G Conaghan, Philip S Helliwell

Background: Treat to Target in psoriatic arthritis (PsA) recommendations have stated that the target should be remission or inactive disease. Potential definitions include Very Low Disease Activity (VLDA), PsA Disease Activity Score (PASDAS) near remission, Disease Activity in PsA (DAPSA) or clinical DAPSA remission. Our aim was to investigate the proportion of patients who fulfil these definitions and how much residual active disease remained.

Methods: This analysis used two datasets: firstly, trial data from the Tight Control of PsA (TICOPA) study which included 206 patients with recent onset (<2 years) PsA receiving standard and biological DMARDs; and secondly an observational clinical dataset from Italy of patients receiving biological DMARDs. Proportions achieving each of the four potential targets were calculated in each dataset and comparisons between treatment groups were performed in the TICOPA dataset. Levels of residual disease were established for key clinical domains of PsA.

Results: All measures could differentiate the TICOPA trial treatment groups ($p < 0.03$). Lower proportions of patients fulfilled the VLDA criteria compared to DAPSA or cDAPSA remission. PASDAS results were different between the cohorts. Residual active disease was low across all definitions although higher levels were seen in DAPSA and cDAPSA compared to VLDA, particularly for psoriasis. In all measures, the proportion with elevated CRP was similar and low.

Conclusion: VLDA appears the most stringent measure. It ensures that significant active arthritis, enthesitis and psoriasis are not present in contrast with DAPSA and PASDAS where composite scores can 'hide' active disease in some domains. **Key index terms** – psoriatic arthritis, treat to target, outcome measures,

Institutions

Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK and Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK.

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford UK.

Dipartimento di Medicina e Scienze della Salute “Vincenzo Tiberio”, Università degli Studi del Molise, Campobasso, Italy

Dr Laura C Coates, MBChB, MRCP (UK), PhD, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK and Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK and Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford UK. Laura.coates@ndorms.ox.ac.uk

Prof Ennio Lubrano, Associate Professor of Rheumatology and Consultant Rheumatologist, MD, PhD. Dipartimento di Medicina e Scienze della Salute “Vincenzo Tiberio”, Università degli Studi del Molise, Campobasso, Italy. enniolubrano@hotmail.com

Dr Fabio Massimo Perrotta, Clinical Research Fellow, MD. Dipartimento di Medicina e Scienze della Salute “Vincenzo Tiberio”, Università degli Studi del Molise, Campobasso, Italy
f.perrotta85@gmail.com

Professor Paul Emery, Professor of Rheumatology, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK and Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK. P.emery@leeds.ac.uk

Professor Philip G Conaghan, Professor of Musculoskeletal Medicine, MB BS, PhD, FRACP, FRCP. Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK and Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK.
P.conaghan@leeds.ac.uk

Dr Philip S Helliwell, Senior Lecturer, MA, MD PhD. Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK and Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK. P.helliwell@leeds.ac.uk

Funding statement – The TICOPA study was funded by Arthritis Research UK (grant number 18825). Laura Coates is funded by a National Institute for Health Research Clinician Scientist award. The research is also supported by the National Institute for Health Research (NIHR) Leeds and Oxford Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The research team acknowledges the support of the Comprehensive Clinical Research Network in supporting this research.

Trial registration - The TICOPA trial was registered with ClinicalTrials.gov, number NCT01106079, and the ISCRCTN registry, number ISCRCTN30147736, registered 15th April 2010.

Competing interests – The authors declare that they have no competing interests.

Corresponding author

Dr Philip S Helliwell

Leeds Institute of Rheumatic and Musculoskeletal Medicine

University of Leeds

2nd Floor, Chapel Allerton Hospital

Harehills Lane

Leeds, LS7 4SA

Tel - +44 113 392 3064

Fax - +44 113 392 4991

Email – p.helliwell@leeds.ac.uk

Footline – Comparing PsA remission targets

Background

In 2013, an international taskforce published recommendations for treating to target in spondyloarthritis (SpA) including psoriatic arthritis (PsA)(1). They recommended that “a major treatment target should be clinical remission/inactive disease of musculoskeletal involvement (arthritis, dactylitis, enthesitis, axial disease)” and that “Clinical remission/inactive disease is defined as the absence of clinical and laboratory evidence of significant inflammatory disease activity.” (1)

Since then, the tight control of PsA (TICOPA) study has shown that treating to target using the minimal disease activity (MDA) criteria improves clinical and patient reported outcomes in PsA despite an increase in drug-related adverse events(2). However the MDA criteria encompass both remission and low disease activity and are not analogous with clinical remission/inactive disease.

Potential remission targets in PsA would be very low disease activity (VLDA) defined as meeting all 7 minimal disease activity (MDA) cut points(3), Disease Activity in PsA (DAPSA) remission (≤ 4) (4) or PASDAS near remission (≤ 1.9) (3). VLDA and PASDAS are designed as composite measures of psoriatic disease, whilst DAPSA is a measure of peripheral arthritis disease activity only. The aim was to investigate which patients fulfil definitions of VLDA and remission, how they compare and how much residual disease is present.

Methods

Two datasets were used: Data from the Tight Control of PsA (TICOPA) randomised controlled trial (RCT) (2); and data from a “real-life” dataset recruited in Italy (University of Molise) (5). The TICOPA trial is a UK multicentre RCT where 206 adults with early PsA were randomised 1:1 to tight control aiming for minimal disease activity or standard care(2).

The Italian dataset included 141 patients with PsA undergoing standard therapy and follow-up. This analysis included only the 79 who were receiving biological therapy (25 adalimumab, 38 etanercept

and 16 golimumab), with or without concomitant DMARDs with at least 6 months follow up (5). These patients were 50.6% male with a mean age (SD) of 53 years (1.3) and mean disease duration (SD) of 6.6 (3.1) years. Appropriate ethical approval was granted for both studies by the Northern and Yorkshire Research Ethics Committee in the UK (TICOPA ref: 07/H0903/72) and by the Comitato Tecnico Scientifico dell'Università degli Studi del Molise, Campobasso, Italy (Italian dataset). All patients consented to be involved in the respective studies.

Four potential definitions of remission/inactive disease were used:

1. Very low disease activity (VLDA)(3) where all 7 of the MDA cut points are met: tender joint count (TJC) \leq 1; swollen joint count (SJC) \leq 1; enthesitis count \leq 1; psoriasis area and severity index (PASI) \leq 1; patient global visual analogue scale (VAS) \leq 20mm; patient pain VAS \leq 15mm; and health assessment questionnaire \leq 0.5.
2. DAPSA remission(4) where $DAPSA \leq 4$ (TJC + SJC + patient global VAS (cm) + pain VAS (cm) + C reactive protein (CRP) (mg/l)
3. Clinical DAPSA remission(4) where $DAPSA \leq 4$ (TJC + SJC + patient global VAS + pain VAS)
4. Near remission in the psoriatic arthritis disease activity score (PASDAS)(3) where $PASDAS \leq 1.9$. PASDAS is calculated as $((0.18 \times \text{physician global VAS}) + (0.159 \times \text{patient global VAS}) - (0.253 \times \sqrt{\text{SF36-PCS}}) + (0.101 \times \text{LN (SJC+1)}) + (0.048 \times \text{LN (TJC+1)}) + (0.23 \times \text{LN (Leeds enthesitis index +1)}) + (0.37 \times \text{LN (tender dactylitis count+1)}) + (0.102 \times \text{LN (CRP+1)}) + 2) \times 1.5$.

Statistical methods

Full data to calculate the composite PsA disease activity index (CPDAI) were not available and so this definition was not included. In the both datasets, the PASDAS was calculated using an imputed measure as SF36 was not collected in the trial(6). Proportions achieving each criteria were calculated. Only patients with full data were included in the comparison. Comparisons between treatment groups in the TICOPA study was performed using chi squared. The agreement between the tested definitions was established using 2x2 tables, Cohen's kappa percentage exact agreement

(PEA). The proportion of residual disease was established for key clinical domains of PsA (peripheral arthritis, enthesitis, psoriasis, dactylitis) and levels of systemic inflammation, as measured by c-reactive protein (CRP), were assessed.

Results

At the end of the TICOPA study (48 weeks), 50 patients (24.3%) were in DAPSA remission, 56 (27.2%) were in cDAPSA remission, 49 (23.8%) were in PASDAS remission and 27 (13.1%) met VLDA.

However missing data precluded calculation for DAPSA in 34 patients, cDAPSA in 23 and VLDA in 24 patients. For fair comparison subsequent statistics are based on those with full data for all measures (n=170)

The difference in proportion of patients achieving all definitions was significant between tight control and standard care ($p < 0.03$, see table 1) in the TICOPA study. In Italy, at 6 months follow up, 18 patients (22.7%) were in DAPSA remission, 22 (27.8%) were in cDAPSA remission, 13 (16.5%) were in PASDAS remission and 15 (18.9%) were in VLDA.

There was a very high agreement found between DAPSA and cDAPSA remission (Cohens Kappa 0.931, 95% CI 0.87, 0.99, $p < 0.001$ in TICOPA, 0.86, 95% CI 0.76, 0.97 in Italy) reflecting their similar components. The agreement was lower but still moderate-substantial between VLDA and both DAPSA remission definitions; VLDA agreement with both DAPSA and cDAPSA remission in TICOPA was 0.57 (95% CI 0.43, 0.71) and 0.52 (95% CI 0.38, 0.65) respectively and in Italy the kappa was 0.66, 95% CI 0.48, 0.83 and 0.60, 95% CI 0.42-0.77 respectively. PASDAS remission showed similar strength agreement with all other measures (in TICOPA - DAPSA rem 0.66 (95% CI 0.53, 0.78), cDAPSA rem 0.60 (95% CI 0.47, 0.73), VLDA 0.58 (95% CI 0.44, 0.73); In Italy - DAPSA rem 0.66, 95% CI 0.45, 0.87, cDAPSA rem 0.55, 95% CI 0.37, 0.72 and VLDA 0.56, 95% CI 0.33, 0.83).

At an individual patient level, there was good agreement between VLDA and DAPSA/cDAPSA remission with a PEA of 84.7/81.8% respectively in TICOPA and 86.1/83.4 in Italy. However this was partially driven by the numbers not fulfilling either target. In TICOPA, there were 25 people in DAPSA remission and 30 in cDAPSA remission who did not meet VLDA. For most of these, the patients fulfilled 6 of the criteria with residual disease activity in one domain (skin n=16, enthesitis n=5, tender joints n=2 and active swollen joints n=3). Three patients did not fulfil 2 domains (swollen joints/skin n=1, tender joints/skin n=1 and tender joints/HAQ n=1). One patient only fulfilled 3/7 MDA domains. In these cases, disease activity was over the VLDA threshold for the individual measures but if the other DAPSA components were low (eg 2 swollen but non-tender joints) then DAPSA remission could still be achieved. In contrast only 1 person was not in DAPSA remission (DAPSA score 4.8) but in VLDA. In Italy, there were 6 people in DAPSA remission and 10 in cDAPSA remission who were not in VLDA. The residual disease activity for both groups was in one domain, for those in DAPSA remission but not VLDA (skin n=5, HAQ=1) and those in cDAPSA (skin n=5, HAQ=2, Pain Vas=3). In contrast only 3/2 people were not in DAPSA/cDAPSA remission but in VLDA.

When considering PASDAS remission, scores showed good agreement with PEA of 86.4% for VLDA and 86.5/83.5% for DAPSA/cDAPSA remission. In Italy PEAs for VLDA and DAPSA/cDAPSA remission were 86.8 /93.4/89.5% respectively. Again these are driven by patients fulfilling neither target.

Using the TICOPA dataset, VLDA seems more stringent with only 4 patients in VLDA with a PASDAS score of >1.9 but 19 patients in PASDAS remission who did not meet VLDA. When comparing DAPSA and PASDAS, it was more common for patients to be in DAPSA remission but not PASDAS remission (n=16 for DAPSA and n=21 for cDAPSA) than it was for patients to be in PASDAS remission without meeting DAPSA (n=7 for DAPSA remission and n=7 for cDAPSA remission).

Levels of residual active disease in patients meeting the remission/very low disease activity criteria are shown in tables 2 and 3. All definitions had similar proportions of residual disease, except for

residual psoriasis in TICOPA which was excluded by VLDA but highest in DAPSA remission (34% with PASI>1) and moderate in PASDAS remission (22% with PASI>1). All definitions had similar proportions of patients with raised CRP levels despite it not being included in either VLDA or cDAPSA definitions.

Conclusions

This analysis reports the first comparison of potential remission targets in PsA. All were able to differentiate significantly between treatment groups in the RCT. Whilst similar proportions of patients fulfilled the DAPSA and cDAPSA remission, fewer people fulfilled the VLDA criteria suggesting that they are more stringent. The differences were predominantly due to active psoriasis but in a few patients residual arthritis and enthesitis was seen in DAPSA or cDAPSA remission in the TICOPA cohort. The PASDAS remission criteria showed variable results with higher proportions achieving the criteria in TICOPA compared to VLDA but with the highest level of residual arthritis. Whilst in the Italian cohort, PASDAS showed similar results to VLDA, with low levels of residual disease.

This retrospective analysis provides important data comparing different treatment targets in PsA allowing direct comparison. Unfortunately we do not have health state “anchor” questions for either patient or physician for comparison. Further work is needed to establish the optimal level of disease control balancing beneficial long term outcome with potential risk of therapy and incorporating physician and patient opinion. Additional analysis in other datasets would aid this debate by providing evidence on whether treating to remission targets such as VLDA is superior to treating to MDA as in the TICOPA trial in terms of disease impact and radiographic outcomes and how this impacts on the prevalence of treatment-related adverse events.

PASDAS and VLDA were developed as multidimensional measures including different domains of psoriatic disease to reflect overall disease activity in a multisystem disease. In contrast the DAPSA focuses particularly on peripheral arthritis and does not include other domains as the developers wanted to devise a unidimensional measure that would assess one element of the disease only(7). This explains some of the mismatch between DAPSA remission and VLDA/PASDAS as residual active skin disease was present. This highlights the need for a separate skin measure to also be used alongside DAPSA if this is chosen over a multidimensional definition to ensure that face validity is maintained for these patients. Interestingly residual dactylitis activity was identified in three patients although the joint counts in the measures should have identified this. Further instructions may be useful to highlight that tender/swollen dactylitic digits should also be recorded in the joint counts.

Examining residual active disease highlighted a potential issue with DAPSA and PASDAS scores, as composites, compared to the approach of VLDA, where individual items are assessed separately rather than summed together. As both DAPSA and PASDAS sum their scores into one final number the balance of scores for each domain can 'hide' active disease in some domains. In both the DAPSA and the PASDAS, higher levels of residual active disease were seen, particularly in the TICOPA cohort. For PASDAS this may reflect the fact that the patient reported domains are more heavily weighted than clinical measurements. In VLDA, as all items are required to meet an individual cut point, residual active disease is limited. Whilst fewer people fulfil this definition, the lower levels of residual disease activity increase its face validity for the concept of "remission".

Two of the scores require a CRP (DAPSA and PASDAS). These data suggests that the inclusion of a laboratory marker is unnecessary as a similar proportion of patients have raised CRP levels in all definitions. This has a practical advantage making target assessment easier in clinical practice. VLDA includes a measure of function as the items within it were taken from the PsA core set(8) following the development methodology of the RA MDA criteria(9). This is a potential limitation of the VLDA as

HAQ can be affected by non-reversible damage as well as disease activity. In these cohorts however, very few patients failed to achieve VLDA due to HAQ alone. For patients with significant damage, it may only be possible to achieve 6 of the 7 cut points (excluding HAQ) but they would still be classified as being in MDA thus fulfilling the T2T recommendations using the alternative target(7).

All these measures require patient and physician reported items. PASDAS is the most involved requiring a complex formula including joint, enthesitis and dactylitis counts, physician global, patient global, short form-36 physical component score and CRP. This may be less feasible for clinical use although apps or spreadsheets can be used. Both DAPSA and VLDA scores are simpler to calculate both requiring a full 66/68 joint count, a patient pain and global VAS. In addition MDA requires assessment of enthesitis and skin. Whilst this does slightly increase the time for assessment, enthesitis can be assessed alongside the joint examination (Leeds enthesitis index is only 6 sites) and the skin item is quickly classified as ≤ 3 palms of body area covered or greater.

The weighted PASDAS retains more dependence on patient reported outcomes and less on clinical measures and, like the DAPSA, depends on a laboratory biomarker which may decrease feasibility. Both cDAPSA and VLDA can be performed relatively easily in routine clinical practice and perform well without the inclusion of an inflammatory blood marker. Neither needs a complex formula and in fact there is a significant overlap between their items. Whilst both are associated with improved outcomes, VLDA is a more stringent measure in keeping with the concept of remission; the brief assessment of enthesitis and skin disease ensure that other domains outside peripheral arthritis are not missed, and its individual cut points for different domains ensure very low levels of residual active disease across all key domains.

This study compared different remission definitions and has shown that all could differentiate between treatment groups in a clinical trial (TICOPA) but VLDA was associated consistently with the lower levels of residual disease activity supporting its face validity as a definition of remission in PsA.

Abbreviations

cDAPSA	Clinical disease activity in psoriatic arthritis
CPDAI	Composite psoriatic disease activity index
CRP	C reactive protein
DAPSA	Disease activity in psoriatic arthritis
DMARDs	Disease modifying anti-rheumatic drugs
HAQ	Health assessment questionnaire
LDA	Low disease activity
MDA	Minimal disease activity
PASDAS	Psoriatic arthritis disease activity score
PASI	Psoriasis area and severity index
PEA	Percentage exact agreement
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
SD	Standard deviation
SJC	Swollen joint count
SpA	spondyloarthritis
TICOPA	Tight control of psoriatic arthritis
TJC	Tender joint count
VAS	Visual analogue score
VLDA	Very low disease activity

Ethical Approval and Consent to participate

Appropriate ethical approval was granted for both studies by the Northern and Yorkshire Research Ethics Committee in the UK (TICOPA ref: 07/H0903/72) and by the Comitato Tecnico Scientifico dell'Università degli Studi del Molise, Campobasso, Italy (Italian dataset). All patients consented to be involved in the respective studies.

Consent for publication

Appropriate ethical approval was granted for both studies by the Northern and Yorkshire Research Ethics Committee in the UK (TICOPA ref: 07/H0903/72) and by the Comitato Tecnico Scientifico dell'Università degli Studi del Molise, Campobasso, Italy (Italian dataset). All patients consented to future publications of the data from respective studies.

Availability of supporting data

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests relevant to this publication.

Funding

The TICOPA study was funded by Arthritis Research UK (grant number 18825). Laura Coates is an NIHR Clinician Scientist. The research is also supported by the National Institute for Health Research

(NIHR) Leeds and Oxford Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The research team acknowledges the support of the Comprehensive Clinical Research Network in supporting this research.

Authors' contributions

LC - study design, data collection, data analysis, data interpretation, writing

EL - study design, data collection, data analysis, data interpretation, writing

FM - study design, data collection, data analysis, data interpretation, writing

PE - study design, data collection, data analysis, data interpretation, writing

PC - study design, data collection, data analysis, data interpretation, writing

PSH - study design, data collection, data analysis, data interpretation, writing

All authors reviewed and approved the final manuscript prior to publication.

References

1. Smolen JS, Braun J, Dougados M, Emery P, Fitzgerald O, Helliwell P, et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: Recommendations of an international task force. *Ann Rheum Dis* 2014;73:6-16.
2. Coates LC, Moverley AR, McParland L, Brown S, Navarro-Coy N, O'Dwyer JL, et al. Effect of tight control of inflammation in early psoriatic arthritis (ticopa): A uk multicentre, open-label, randomised controlled trial. *Lancet* 2015;386:2489-98.
3. Coates LC, Helliwell PS. Defining low disease activity states in psoriatic arthritis using novel composite disease instruments. *J Rheumatol* 2016;43:371-5.
4. Schoels MM, Aletaha D, Alasti F, Smolen JS. Disease activity in psoriatic arthritis (psa): Defining remission and treatment success using the dapsa score. *Ann Rheum Dis* 2016;75:811-8.
5. Perrotta FM, Marchesoni A, Lubrano E. Minimal disease activity and remission in psoriatic arthritis patients treated with anti-tnf-alpha drugs. *J Rheumatol* 2016;43:350-5.
6. Coates LC, Mahmood F, Emery P, Conaghan PG, Helliwell PS. The dynamics of response as measured by multiple composite outcome tools in the tight control of inflammation in early psoriatic arthritis (ticopa) trial. *Ann Rheum Dis* 2017;76:1688-92.
7. Smolen JS, Schols M, Braun J, Dougados M, FitzGerald O, Gladman DD, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. *Ann Rheum Dis* 2017.
8. Gladman DD, Mease PJ, Strand V, Healy P, Helliwell PS, Fitzgerald O, et al. Consensus on a core set of domains for psoriatic arthritis. *J Rheumatol* 2007;34:1167-70.
9. Wells GA, Boers M, Shea B, Brooks PM, Simon LS, Strand CV, et al. Minimal disease activity for rheumatoid arthritis: A preliminary definition. *J Rheumatol* 2005;32:2016-24.