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Real World Validation of the Minimal Disease Activity Index in Psoriatic Arthritis: An Analysis from a Prospective, Observational, Biological Treatment Registry

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Structured Abstract

Objectives: To describe the minimal disease activity (MDA) rate over time in psoriatic arthritis (PsA) patients receiving anti-TNF agents, evaluate prognostic factors of MDA achievement, and identify the most common unmet criteria among MDA achievers.

Design: Biologic Treatment Registry Across Canada (BioTRAC): ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis, ankylosing spondylitis, or PsA with Infliximab (IFX), Golimumab (GLM) or ustekinumab.

Setting: 46 primary-care Canadian rheumatology practices.

Participants: 223 PsA patients receiving IFX (enrolled since 2005) and GLM (enrolled since 2010) with available MDA information at baseline, 6 months, and/or 12 months.

Primary and secondary outcome measures: MDA was defined as ≥5 of the following criteria: Tender Joint Count (TJC)-28 ≤1, Swollen Joint Count (SJC)-28 ≤1, Psoriasis Area Severity Index (PASI) ≤1, or Body Surface Area ≤3, Pain (VAS) ≤15mm, Patient's global assessment (PtGA) (VAS) ≤20mm, HAQ ≤0.5, tender entheseal points ≤1. Independent prognostic factors of MDA achievement were assessed with multivariate logistic regression.

Results: MDA was achieved by 11.7% of patients at baseline, 43.5% at 6 months, 44.8% at 12 months, and 48.8% at either 6 or 12 months. Among MDA achievers at 6 months, 75.7% sustained MDA at 12 months. Lower baseline HAQ (OR=0.210; 95% CI: 0.099-0.447) and lower TJC28 (OR=0.880; 95% CI: 0.804-0.964), were significant prognostic factors of MDA achievement over 12 months of treatment. The most commonly unmet MDA criteria among MDA achievers was patient reported pain (25%), PtGA (15%) and PASI (12%).

Conclusions: Almost 50% of patients treated with IFX or GLM in routine clinical care achieve MDA within the first year of treatment. Lower baseline HAQ and lower TJC28, were identified as significant prognostic factors of MDA achievement. The most commonly unmet criteria in patients who achieved MDA were pain, PtGA and PASI.

Trial Registration: NCT00741793, "Biologic Treatment Registry Across Canada (BioTRAC)"

Strengths and limitations of this study:

- The limitations in the current study are that the peripheral joint activity was measured using the 28 tender/swollen joint count although the Outcome Measures in Rheumatology Clinical Trials (OMERACT) recommends the measure of 68 tender/66 swollen joint counts.
- Furthermore, although several approaches were used to assess disease activity, radiographic images are not collected in BioTRAC, therefore not allowing the examination of radiographic progression.
- There is also potential bias given the observational nature of the study, a bias that is avoided when using data from clinical trials.
- The strength of the study is that patients were seen in a real world setting by Canadian rheumatologists during routine clinical practice which enhances the generalizability of the results to the target population.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic systemic inflammatory musculoskeletal disease characterized by synovitis, axial disease, enthesitis, or dactylitis, and psoriasis. It is variably associated with other extra-articular manifestations that affects women and men equally.[1] PsA also affects up to 30 to 40% of patients with psoriasis.[2] Previously PsA was considered a mild disease; however, evidence from the last two decades has shown that it is frequently an erosive and deforming in 40 to 60% of patients who are diagnosed within the first few years.[3-5] Furthermore, similarly to other rheumatic diseases such as rheumatoid arthritis (RA), PsA has been associated with impaired physical function, reduced quality of life, and increased mortality,[6-8] with about 20% of patients eventually developing a highly destructive and disabling form of PsA.[9] Manifestations of PsA contribute to disease burden due to the negative effects on the patient's psychological and psychosocial functioning, dissatisfaction with the management of the disease and the negative impact on daily living activities.[10]

Over the years, major clinical improvements have been achieved in the outcome of inflammatory rheumatic diseases due to improved treatment availability and more commonly adopted early treatment algorithms including the treat to target strategy which has become the standard of care for newly diagnosed patients in RA.[11,12] Treatment therapies in PsA such as tumor necrosis factor α blockers (anti TNF α), have demonstrated a reduction in disease activity and radiographic progression of joint damage.[13-15] Although remission remains the ultimate treatment goal, the complexity of PsA makes it difficult to identify valid criteria that mark a state of remission or low disease activity that take into account all dimensions of the clinical manifestations of the disease. In the past decades, different scores were used to evaluate the disease severity of PsA such as the Disease Activity Score using 28 joints (DAS28) originally developed for RA assessment, as well as the Psoriatic Arthritis Disease Activity Score

(PASDAS), a weighted index comprising assessments of joints, function, acute-phase response, quality of life (QOL), and patient and physician global VAS scores, and the Composite Psoriatic Disease Activity Index (CPDAI) which takes into account the assessment of different domains such as peripheral arthritis, skin disease, spinal disease, dactylitis, and enthesitis. The minimal disease activity (MDA) was developed to take into account the heterogeneity seen and measure the disease activity of several clinical domains which is a more suitable outcome measure compared to DAS28 which does not take into consideration the full spectrum of disease manifestations.[16] These MDA criteria were validated in randomized controlled trials and observational studies demonstrating that patients who achieved MDA for a period of 12 months or more experienced a reduction in radiographic joint damage progression.[17,18] The tight control of inflammation in early psoriatic arthritis (TICOPA) trial was the first randomised, controlled trial, with a treat to target approach in PsA patients where the tight control group were reviewed every 4 weeks with escalation of treatment if MDA criteria wasn't met. Patients in the tight control group showed significant improvements in joint and skin disease activity, as well as benefits in function and QOL compared to the standard of care group.[19] However as far as we know, no real world evidence data on MDA are available in the literature.

The aim of the current study is to 1) describe the rate of MDA achievement over time, 2) evaluate prognostic factors of MDA achievement, 3) assess which unmet criteria were more common among patients who achieved MDA, 4) evaluate which unmet criteria were more common among patients who were near MDA achievers, and 5) assess DAS28 remission, DAS28 deep remission, and the level of agreement between MDA and DAS28 remission in PsA patients treated with infliximab or golimumab, in a routine clinical practice setting. The analysis was done using data from the Biologic Treatment Registry Across Canada (BioTRAC), an

ongoing, community based, Canada-wide, multi-centre, prospective, observational registry of patients with inflammatory arthritis.

METHODS

Study design

BioTRAC is an ongoing Canadian multi-centre, prospective, observational registry collecting real world clinical, laboratory, patient-centric, and safety data in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis patients treated with infliximab (IFX), golimumab (GLM), or ustekinumab as part of their routine care. The historical development of the registry has been described by Thorne et al.[20] To date there are over 100 rheumatology sites, participating, both in an institutional and private setting, with over 2100 patients enrolled in the programme across all indications. In accordance with the observational nature of the registry, there is no protocol-defined intervention in patient management. All clinical decisions and treatments are based on routine practice and the judgement of the treating physicians. Patients provided written informed consent prior to participation in the study. Ethics approval for participation in the BioTRAC program was obtained from the respective Research Ethics Boards (REB) of participating institutional sites and a Central Institutional Review Board (IRB Services, Ontario Canada) for private practice sites. BioTRAC is conducted according to the tenets of the Declaration of Helsinki.

Study population

Biologic-naïve patients or patients previously treated with one biologic who are eligible for treatment with infliximab, golimumab, or ustekinumab as per their respective Canadian Product Monograph are considered for inclusion in the registry. For the purpose of the current analysis, 223 patients with PsA treated with infliximab (enrolled since 2005) or with golimumab (enrolled

since 2010) were included from 46 primary care rheumatology practices across Canada. All efficacy analyses were observed and included all enrolled PsA patients who received at least one dose of IFX or GLM, and had at least one follow up assessment with available MDA data at 6 or 12 months. Figure 1 represents the flow chart of the patient population over time.

Data collection

The following clinical/laboratory parameters and patient reported outcomes (PROs) are collected as per routine care at baseline and at all follow up visits, with suggested assessments every six months given that this is within acceptable practice patterns for patients with active PsA: morning (AM) stiffness, swollen joint count (SJC28), tender joint count (TJC28), patient's (PtGA), and physician's (MDGA) global assessment of disease activity, health assessment questionnaire (HAQ), patient's assessment of pain, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

Statistical Analysis

Descriptive statistics included mean and standard deviations for continuous variables, and proportions for categorical variables. The absolute improvement in disease parameters at 6 and 12 months of treatment was assessed with the non-parametric Wilcoxon Signed Ranks test, while between group differences for continuous and categorical variables were assessed with the non-parametric Kruskal-Wallis test and the Pearson Chi-square test, respectively. The improvement in MDA achievement, DAS28 remission (<2.6), and DAS28 deep remission (<1.98) over time was assessed for statistical significance with the McNemar test. Independent prognostic factors of MDA achievement at 6 or 12 months of treatment were assessed with backward conditional logistic regression; covariates considered were: province, gender, age, baseline biologic agent, MDGA, PtGA, pain, HAQ, SJC28, TJC28, and enthesitis count with probability for stepwise entry and removal at the 0.05 and 0.10 level, respectively. MDA was defined as the fulfillment of

≥5 of the following criteria: TJC28≤1, SJC28≤1, PASI≤1, pain (VAS) ≤15 mm, PtGA (VAS) ≤20 mm, HAQ≤0.5, tender entheseal points ≤1.[18] Near MDA was defined as fulfillment of 4/7 criteria. Patients with missing information included gender (n=21), age (n=89), disease duration (n=76), while baseline parameters for DAS28 (n=49), MDGA (n=31), CRP (n=51), ESR (n=48), AM stiffness (n=34), and TJC28, SJC28, PtGA, HAQ, pain, PASI (all, n=27). Furthermore 12%, 30%, and 38% of patients had missing MDA at baseline, 6 and 12-month follow-up, respectively (see Figure 1). There was no imputation of missing data in the current analysis. Statistical analyses were conducted with SPSS 21.0 (SPSS Inc., Chicago, IL).

RESULTS

Table 1 summarizes the patient demographics and characteristics by region at baseline. There were 130 (58.3%) and 93 (41.7%) patients on GLM and IFX, respectively. Mean (SD) age and disease duration was 49.8 (11.1) and 5.4 (6.3) years, respectively, and 50% were males. Baseline disease parameters for DAS28, TJC, SJC, pain, PtGA, MDGA, morning stiffness, HAQ, CRP, and ESR were statistically comparable at baseline among Canadian regions. However significant differences between regional groups were observed at baseline for mean (SD) disease duration (p=0.002), enthesitis count [Western: 6.8 (3.3), Ontario: 4.6 (4.2), Quebec: 3.4 (2.1), Maritime: 5.8 (3.6); p=0.012], and PASI [Western: 3.8 (4.2), Ontario: 3.7 (5.4), Quebec: 1.4 (2.9), Maritime: 1.2 (1.5); p<0.001]. Furthermore, use of a previous biologic (p=0.017), previous DMARD (p=0.047), and previous corticosteroid (p=0.006) showed significant between group differences among regions (Table 1).

Table 1. Demographics and disease characteristics by region at baseline

Parameter	Western (N=18)	Ontario (N=111)	Quebec (N=63)	Maritimes (N=31)	p-value	Total (N=223)
Socio-demographics						
Gender, n (%) [a]						
Male	5 (38.5)	44 (43.1)	35 (58.3)	17 (63.0)	0.107	101 (50.0)
Female	8 (61.5)	58 (56.9)	25 (41.7)	10 (37.0)		101 (50.0)
Age (years), mean (SD)	50.7 (14.6)	49.7 (10.7)	51.0 (11.6)	46.5 (9.9)	0.393	49.8 (11.1)
Disease Parameters, mean (SD)						
Disease duration (years)	4.0 (4.6)	5.4 (6.2)	7.5 (7.4)	1.9 (2.0)	0.002	5.4 (6.3)
DAS28	4.3 (0.8)	4.4 (1.7)	4.2 (1.3)	4.3 (1.8)	0.928	4.3 (1.6)
TJC28	8.1 (6.4)	7.1 (6.7)	5.8 (5.0)	9.0 (9.2)	0.555	7.0 (6.7)
SJC28	4.1 (3.8)	4.6 (4.7)	5.2 (4.1)	5.0 (5.1)	0.549	4.8 (4.5)
MDGA (VAS cm)	6.0 (2.1)	5.1 (2.4)	5.5 (2.3)	4.6 (1.4)	0.062	5.2 (2.2)
PtGA (VAS mm)	54.5 (27.1)	52.0 (28.3)	49.5 (22.2)	46.0 (25.6)	0.662	50.5 (26.1)
AM stiffness[b] (min)	54.6 (49.2)	48.1 (47.6)	35.5 (39.8)	49.1 (43.3)	0.237	45.0 (45.0)
HAQ	1.3 (0.5)	1.1 (0.7)	1.1 (0.6)	1.0 (0.7)	0.263	1.1 (0.7)
Pain (VAS mm)	47.9 (23.0)	49.2 (27.5)	48.4 (23.0)	40.7 (23.6)	0.492	47.6 (25.4)
PASI	3.8 (4.2)	3.7 (5.4)	1.4 (2.9)	1.2 (1.5)	<0.001	2.6 (4.4)
Enthesitis count[c]	6.8 (3.3)	4.6 (4.2)	3.4 (2.1)	5.8 (3.6)	0.012	4.9 (3.5)
ESR (mm/h)	14.0 (15.3)	22.5 (22.9)	19.4 (16.4)	19.0 (22.3)	0.566	20.7 (20.7)
CRP (mg/L)	12.4 (13.6)	17.7 (36.9)	10.7 (14.2)	14.1 (27.6)	0.952	14.7 (29.1)
Medications, n (%)						
Baseline Biologic Agent						
GLM	8 (44.4)	69 (62.2)	39 (61.9)	14 (45.2)	0.200	130 (58.3)
IFX	10 (55.6)	42 (37.8)	24 (38.1)	17 (54.8)		93 (41.7)
Previous biologic	3 (21.4)	5 (5.3)	10 (17.2)	7 (24.1)	0.017	25 (12.8)
Previous DMARD	12 (85.7)	59 (62.1)	47 (81.0)	21 (72.4)	0.047	139 (70.9)
Previous corticosteroid	6 (42.9)	17 (17.9)	21 (36.2)	3 (10.3)	0.006	47 (24.0)
Concomitant DMARD	11 (78.6)	52 (54.7)	40 (69.0)	19 (65.5)	0.164	122 (62.2)
Concomitant Methotrexate	4 (28.6)	43 (45.3)	35 (60.3)	16 (55.2)	0.102	98 (50.0)
Concomitant corticosteroid use	1 (7.1)	10 (10.5)	7 (12.1)	2 (6.9)	0.868	20 (10.2)

[a]Percentages based on available data
[b]Capped at 120 minutes.
[c]Among patients with enthesitis.
DAS28, Disease Activity Score; HAQ, Health assessment questionnaire; MDGA, Physician Global Assessment of Disease Activity; PASI, Psoriasis Area and Severity Index; PtGA, Patient Global Assessment of Disease Activity; SJC, Swollen joint count; TJC, Tender joint count; GLM, golimumab; IFX, infliximab.

All disease parameters showed statistically significant improvement over time from baseline to month 6 and month 12 ($p<0.05$) (supplementary material).

Figure 2 describes MDA achievement, DAS28 remission, and DAS28 deep remission over time. At baseline, 6, and 12 months of treatment, 11.7%, 43.5%, and 44.8% of patients achieved MDA, respectively, while 48.8% achieved MDA at 6 or 12 months. Additionally, 34.6% (n=28/81) achieved MDA at both 6 and 12 months of treatment (overall sustained MDA). DAS28 remission (<2.6), was achieved by 14.4%, 50.0%, and 48.8% of patients, and DAS28 deep remission (<1.98), by 8.6%, 33.9%, and 28.6%, at baseline, 6, and 12 months of treatment, respectively (Figure 2). The improvement in MDA achievement, DAS28 remission, and DAS28 deep remission from baseline to 6 months and 12 months was statistically significant for all measures of disease activity ($p<0.05$). Table 2 depicts sensitivity, specificity, positive and negative predictive values between MDA and DAS28 remission as well as DAS28 deep remission. There was substantial agreement between MDA and DAS28 remission with a Kappa measure of agreement of 0.653 ($p<0.001$) while that between MDA and DAS28 deep remission showed moderate agreement with 0.598 ($p<0.001$).

Table 2. Agreement between MDA and DAS28

Diagnostic Criteria Definitions	DAS28 Remission (<2.6)	DAS28 Deep Remission (<1.98)

Sensitivity	70.7%	82.1%
Specificity	92.3%	85.7%
Positive Predictive Value	82.1%	60.4%
Negative Predictive Value	86.4%	94.7%
Kappa agreement (K)	0.653	0.598

Univariate analysis (Table 3A) showed that male gender (p= 0.031) and lower age (p=0.011) were significantly associated with MDA achievement at 6 or 12 months of treatment. Furthermore, significant between-region differences were observed for MDA achievement at 6 or 12 months of treatment (p=0.019). Ontario and Quebec patients had the highest MDA rates with 56.0% and 52.9%, respectively, while 36.4% and 14.3% of patients in Maritime and Western provinces reached MDA, respectively. In addition, significantly lower disease severity was observed at baseline among MDA achievers for the following disease parameters: MDGA (p<0.001), PtGA (p<0.001), pain (p<0.001), HAQ (p<0.001), SJC28 (p=0.001), TJC28 (p<0.001), and enthesitis count (p=0.013). Multivariate logistic regression analysis (Table 3B) showed that lower baseline HAQ (OR=0.210, p<0.001) and lower TJC28 (OR=0.880, p=0.006) were significant prognostic factors of MDA achievement over 12 months of treatment, while parameters of lower enthesitis count (OR=0.838, p=0.069) and GLM as the biologic agent (OR=2.228, p=0.073) showed a trend towards statistical significance.

Table 3A. Univariate Analysis for MDA Achievement at 6 or 12 Months of Treatment

Parameters	**MDA achievement at 6 or 12 months**		**p-value[c]**
	Yes	**No**	
Province, n (%)			

Western	2 (14.3)	12 (85.7)	0.019
Ontario	42 (56.0)	33 (44.0)	
Quebec	27 (52.9)	24 (47.1)	
Maritimes	8 (36.4)	14 (63.6)	
Gender, n (%)			
Male	45 (59.2)	31 (40.8)	0.031
Female	28 (40.6)	41 (59.4)	
Age, mean (SD)	46.6 (12.0)	51.6 (10.7)	0.011
MDGA (VAS cm)[a], mean (SD)	4.3 (2.4)	5.9 (2.0)	<0.001
PtGA (VAS mm)[a], mean (SD)	39.7 (24.7)	56.8 (24.9)	<0.001
Pain (VAS mm)[a], mean (SD)	35.6 (24.4)	55.1 (23.2)	<0.001
HAQ[a], mean (SD)	0.7 (0.6)	1.3 (0.6)	<0.001
SJC28[a], mean (SD)	3.4 (3.8)	5.4 (4.4)	0.001
TJC28[a], mean (SD)	3.8 (4.1)	8.8 (6.8)	<0.001
Enthesitis count[a,b], mean (SD)	0.7 (1.4)	2.0 (3.3)	0.013
Baseline biologic agent			
GLM	48 (53.9)	41 (46.1)	0.158
IFX	31 (42.5)	42 (57.5)	

[a]Denotes disease parameters at baseline.
[b]Among all patients (with and without enthesitis).
[c]P-value was assessed with chi-square for categorical variables or with non-parametric Mann-Whitney U test for continuous variables.

Table 3B. Multivariate Analysis for MDA Achievement at 6 or 12 Months of Treatment

Parameters	Beta	Odds Ratio	95% Confidence Intervals for Odds Ratio		p-value
			Lower	Upper	
Baseline HAQ	-1.561	0.210	0.099	0.447	<0.001
Baseline TJC28	-0.128	0.880	0.804	0.964	0.006
Baseline enthesitis count	-0.177	0.838	0.692	1.014	0.069
Baseline biologic agent: GLM vs. IFX	0.801	2.228	0.929	5.343	0.073

Multivariate analysis was assessed with backward conditional logistic regression, covariates entered were: province, gender, age, baseline biologic agent, MDGA, PtGA, Pain, HAQ, SJC28, TJC28, and enthesitis count with probability for stepwise entry and removal at the 0.05 and 0.10 level, respectively.

Among the patients who achieved MDA at any time point, the highest proportion met all 7 MDA criteria with 45.8%, while 24.4% met 6 /7 criteria, and 29.8% met 5/7 criteria (Figure 3A). The most commonly unmet criteria among these cases were patient-reported pain (with 25.2%), PtGA (with 15.3%), and PASI (with 12.2%) (Figure 3B). Additionally, among the 309 instances of non-MDA achievement, the proportion of cases that achieved near MDA was 16.5% (51/309). The most common reason for non-MDA in near-MDA cases was patient-reported pain (82.4%) followed by PtGA (68.6%), and HAQ (60.8%) (Figure 3C). Interestingly, 9 patients with available data that had reached MDA at 6 months were not in MDA state after 12 months. It was determined that the most common criteria not met in this group were: PtGA (88.9%), enthesitis count (66.7%), TJC (55.6%), and PASI (33.3%).

DISCUSSION

The current analysis is the first community-based Canadian study presenting a 12 month follow up of 223 prospectively followed patients with PsA from the BioTRAC registry. All measures of disease activity in the current study showed a statistical improvement over time ($p<0.05$).

Reported MDA achievement at 6 and 12 months of treatment was comparable with 43.5% and 44.8%, respectively. Among MDA achievers at 6 months, 75.7% (n=28/37) had sustained MDA at 12 months. The MDA achievement rate of approximately 45% is in line with the rates reported by Mease et al. despite the randomized controlled setting of this study.[21] However, our findings are lower in comparison with two recent studies which reported that 64% of the study population achieved MDA after 12 months of treatment with anti TNF α therapy [22,23]. In the current real world setting study, a slightly higher proportion of patients (48.8%) achieved DAS28 remission at 12 months in comparison to MDA achievement. However, the MDA had

substantial and moderate agreement with DAS28 and DAS28 deep remission, respectively. Thus the current analysis revealed that MDA criteria are a more powerful and discriminatory method to assess PsA than DAS28. The simplicity in calculating MDA and the lack of requirement for acute phase reactants at the time of visit as compared to the DAS28, makes the MDA a more desirable and practical tool to measure disease outcome in PsA.

Adjusted analysis of baseline variables showed that lower HAQ, lower TJC28, lower enthesitis count, and GLM as the biologic agent were considered independent prognostic factors of MDA achievement over 12 months of treatment. In addition to HAQ [24,25], previous studies have also identified shorter symptom duration, greater general well-being (global visual analogue scale) [24], younger age, higher C-reactive protein (CRP), and lower BASFI as significant predictors of MDA, which however, were not confirmed in our study.[26] Moreover, other studies have shown that baseline lower HAQ, higher swollen joint count, and no previous use of anti TNF α therapy are also prognostic factors of remission at 12 months of treatment.[27,28]

The current results also showed that the most common limiting factors among patients who achieved MDA were including pain, PtGA, and PASI. Among patients who achieved near-MDA, the most commonly unmet criteria were pain, PtGA, and HAQ. These results highlight the difference in perception of disease activity by physicians and patients in the relative importance placed on specific disease aspects.

All disease parameters showed a statistically significant improvement at 6 months of treatment and were sustained over the 12-month period. In a prospective cohort study by Saber *et al*., statistically significant improvements in clinical outcome measures were also observed for TJC28, SJC28, CRP, and HAQ at 12 months in patients treated with anti TNF α therapy

(p<0.001 for all), wherein statistical improvement was achieved within the first 3 months of treatment.[27]

The limitations of the current study are that the peripheral joint activity was measured using the 28 tender/swollen joint count although the Outcome Measures in Rheumatology Clinical Trials (OMERACT) recommends the measure of 68 tender/66 swollen joint counts.[16] However, simplified joint counts have been shown to be sufficiently sensitive to measure clinical response in PsA patients.[29] Furthermore, although several approaches were used to assess disease activity, radiographic images are not collected in BioTRAC, therefore not allowing the examination of radiographic progression. There is also potential bias given the observational nature of the study, a bias that is avoided when using data from clinical trials. The strength of the study is that patients were seen in a real world setting by Canadian rheumatologists during routine clinical practice which enhances the generalizability of the results to the target population.

In conclusion, our results showed overall improvement in clinical parameters and disease activity in PsA patients treated with infliximab or golimumab during the 2 year follow up. By 6 and 12 months of treatment almost 50% of patients achieved MDA, and among achievers of MDA the most commonly unmet criteria were patient-reported pain, PtGA, and PASI. Furthermore, lower baseline HAQ and lower TJC at baseline, were identified as significant prognostic factors of MDA achievement. This study provides evidence supporting the validity of MDA in real world and its usefulness in patient management under routine clinical care.

FIGURE LEGENDS

Figure 2. MDA Achievement, DAS28 Remission and DAS28 Deep Remission over Time

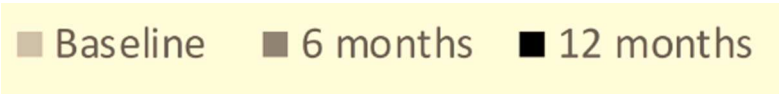
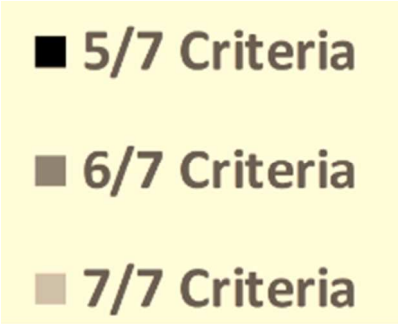


Figure 3A. Proportion of Met Criteria among MDA Achievers



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Competing interests:

Dr. Rahman reports personal fees from Janssen Inc., during the conduct of the study; personal fees from Abbott, AbbVie, Amgen, BMS, Celgene, Novartis, Pfizer, Roche, outside the submitted work. Dr. Zummer, Dr. Chow and Dr. Kapur report personal fees from Janssen Inc., during the conduct of the study. Dr. Bessette reports personal fees from Janssen Inc., during the conduct of the study; personal fees from Amgen, BMS, Roche, UCB, AbbVie, Pfizer, Merck, Sanofi, Celgene, Lilly, Novartis, outside the submitted work. Dr. Baer reports personal fees from Janssen Inc., during the conduct of the study; personal fees from AbbVie, Amgen, BMS, Pfizer, Roche, outside the submitted work. Dr. Haraoui reports personal fees from Janssen Inc., during the conduct of the study; personal fees from AbbVie, Amgen, BMS, Celgene, Pfizer, Roche, UCB, outside the submitted work. Dr. Kelsall reports personal fees from Janssen Inc., during the conduct of the study; personal fees from Abbott, AstraZeneca, BMS, Merck-Schering, Lilly, Pfizer, Wyeth, Roche, Takeda, UCB, outside the submitted work. Dr. Rampakakis and Ms. Psaradellis report personal fees from Janssen Inc. as employees of JSS Medical Research Inc., the CRO hired, during the conduct of the study. Dr. Lehman, Dr. Nantel, Dr. Osborne and Dr. Tkaczyk report personal fees as employees of Janssen Inc., during the conduct of the study.

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Contributorship statement:

Dr. Rahman, Dr. Zummer, Dr. Bessette, Dr. Baer, Dr. Haraoui, Dr. Chow, Dr. Kelsall and Dr. Kapur substantially contributed to the acquisition of the data for the work and revised the manuscript for important intellectual property. Dr. Rampakakis, Dr. Lehman, Dr. Nantel, Dr. Osborne and Dr. Tkaczyk substantially contributed to the conception or design of the work and the interpretation of the data for the work, and revised the manuscript critically for important intellectual content. Ms. Psaradellis substantially contributed to the analysis and interpretation of data for the work and drafted the manuscript. All authors approved the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Role of study sponsor: The sponsor, Janssen Inc., participated in the study design and interpretation of the data and funded all aspects of the study, but did not have an impact on data collection or the decision to submit the article for publication. The writing was conducted by a third party and the sponsor critically reviewed the manuscript.

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Access to data: All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; any discrepancies from the study as planned have been explained.

Data sharing: No additional data available.

Checklist: The criteria described in the STROBE guidelines (checklist) have been satisfied.

What this paper adds:

What is already known on this subject:

- The control of disease activity adopting the treat-to-target strategy or minimal disease activity (MDA) has not been carefully established and is becoming the current challenge in management of PsA.
- As far as we know, there is no real-world evidence data on MDA available in the literature and our study will address this need.

What this study adds:

- The results of the current study showed that almost 50% of patients achieved MDA within the first year of treatment and thus provides evidence supporting the validity of

MDA in Canadian real-world and its usefulness in patient management under routine clinical care.

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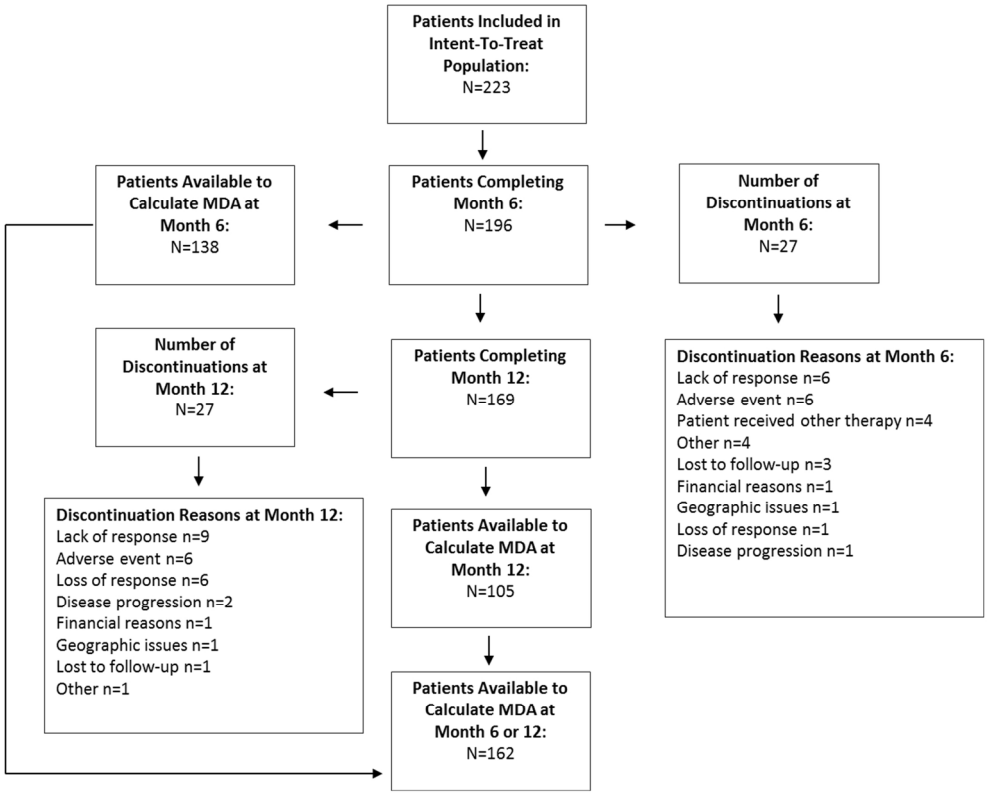

Flow chart of the patient population over time

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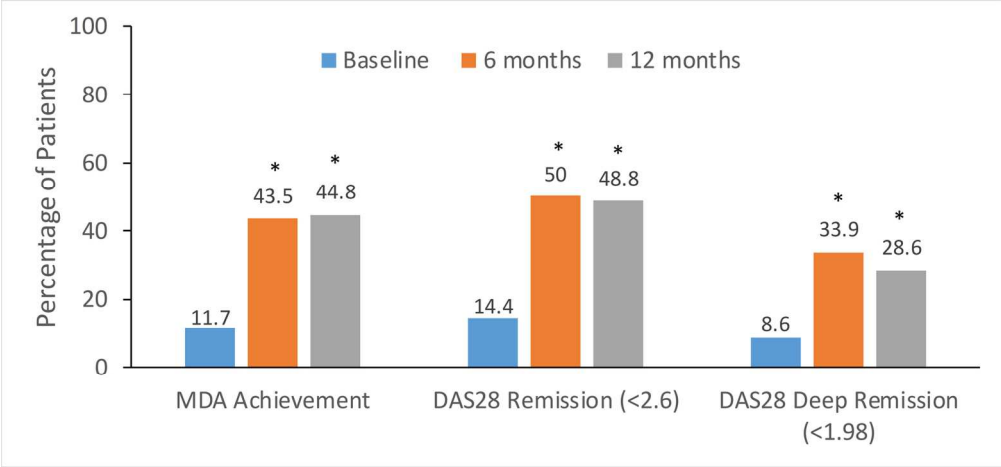

MDA Achievement, DAS28 Remission and DAS28 Deep Remission over Time
*The improvement in MDA achievement, DAS28 remission and DAS28 deep remission from baseline to 6 months and from baseline to 12 months was assessed with the McNemar Test ($p<0.001$ for all, except DAS28 deep remission at 12 months $p=0.019$).

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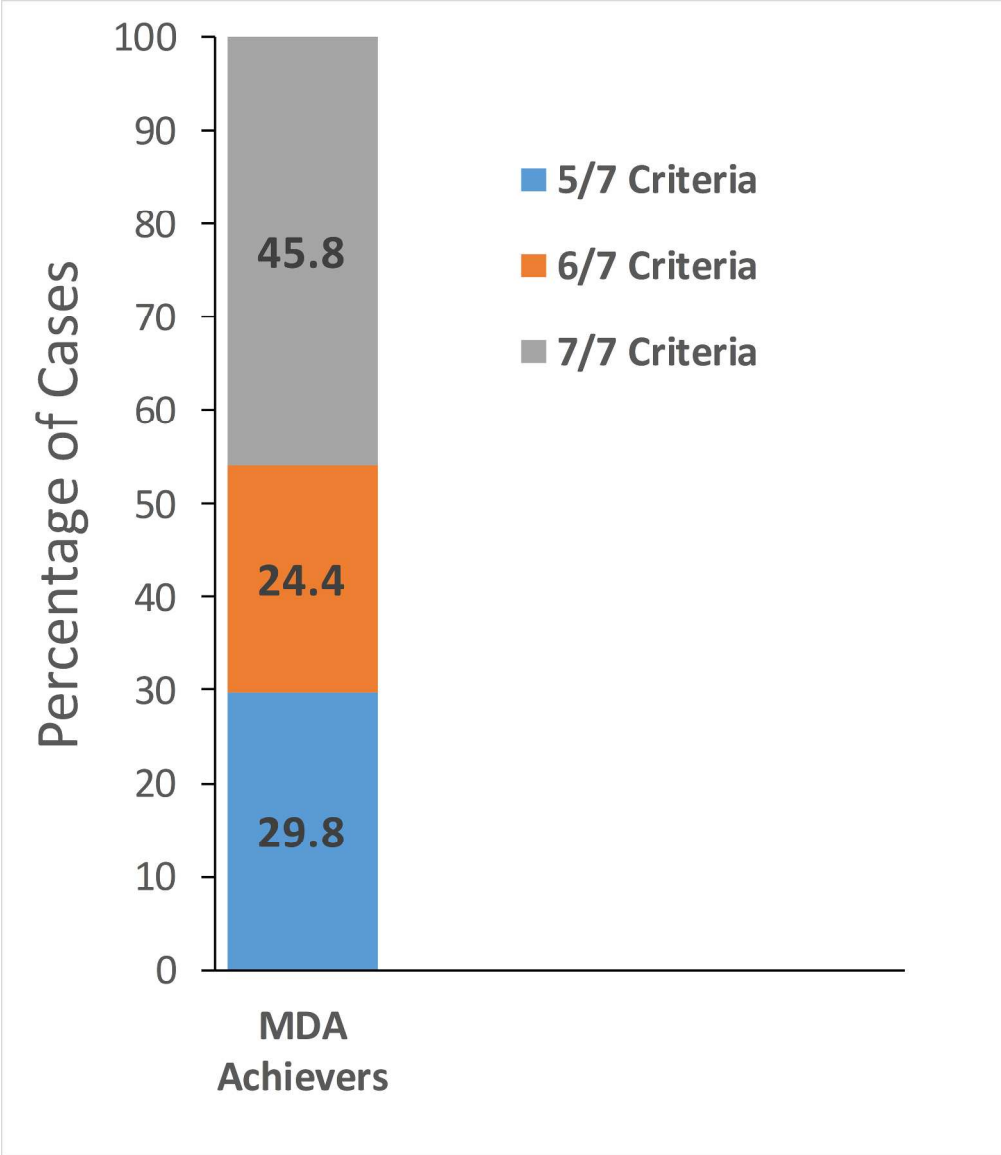

Proportion of Met Criteria among MDA Achievers

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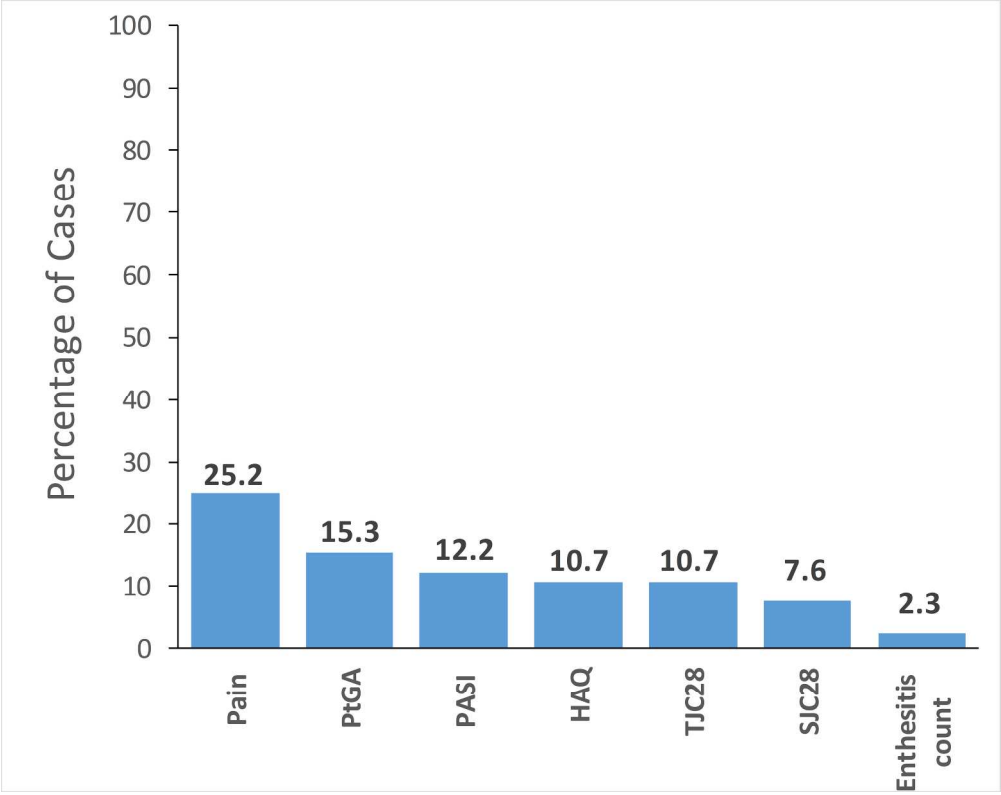

Proportion of Unmet Disease Criteria among MDA Achievers

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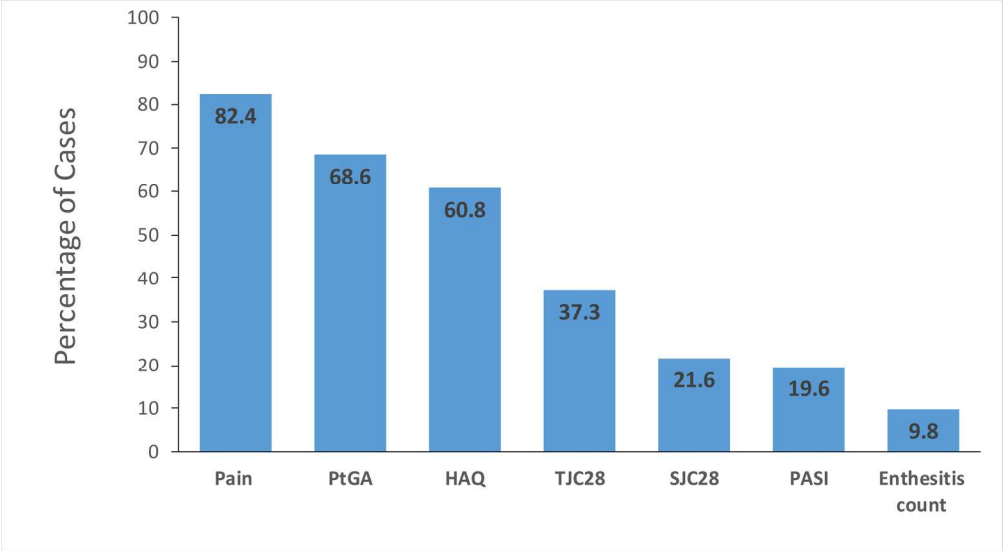

Proportion of Unmet Criteria among New MDA Achievers

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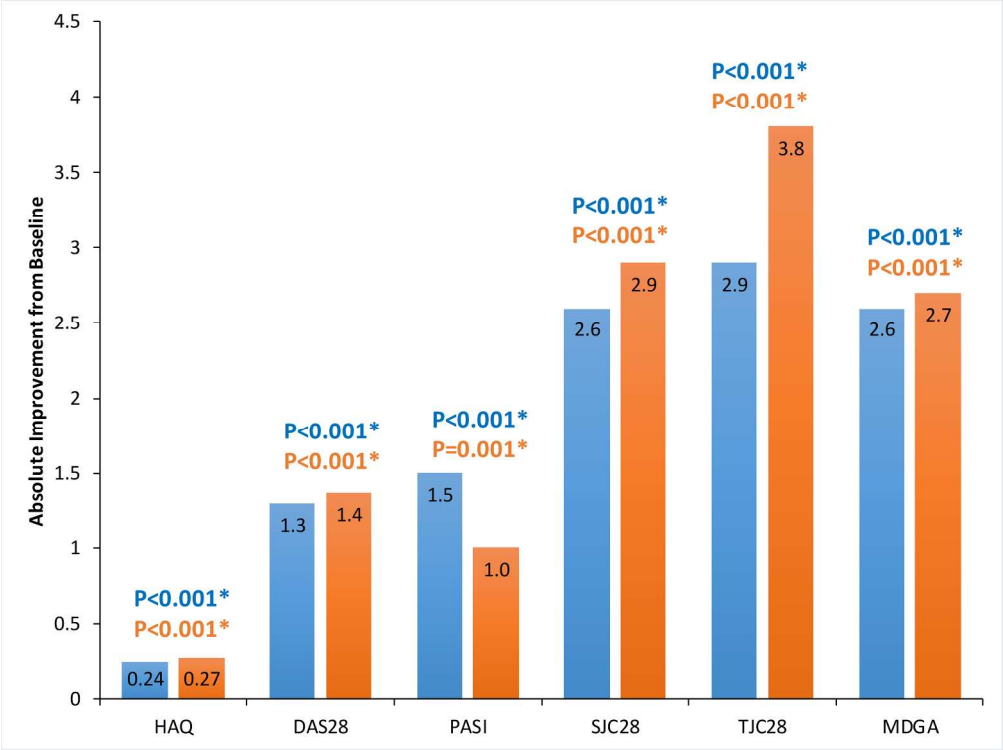

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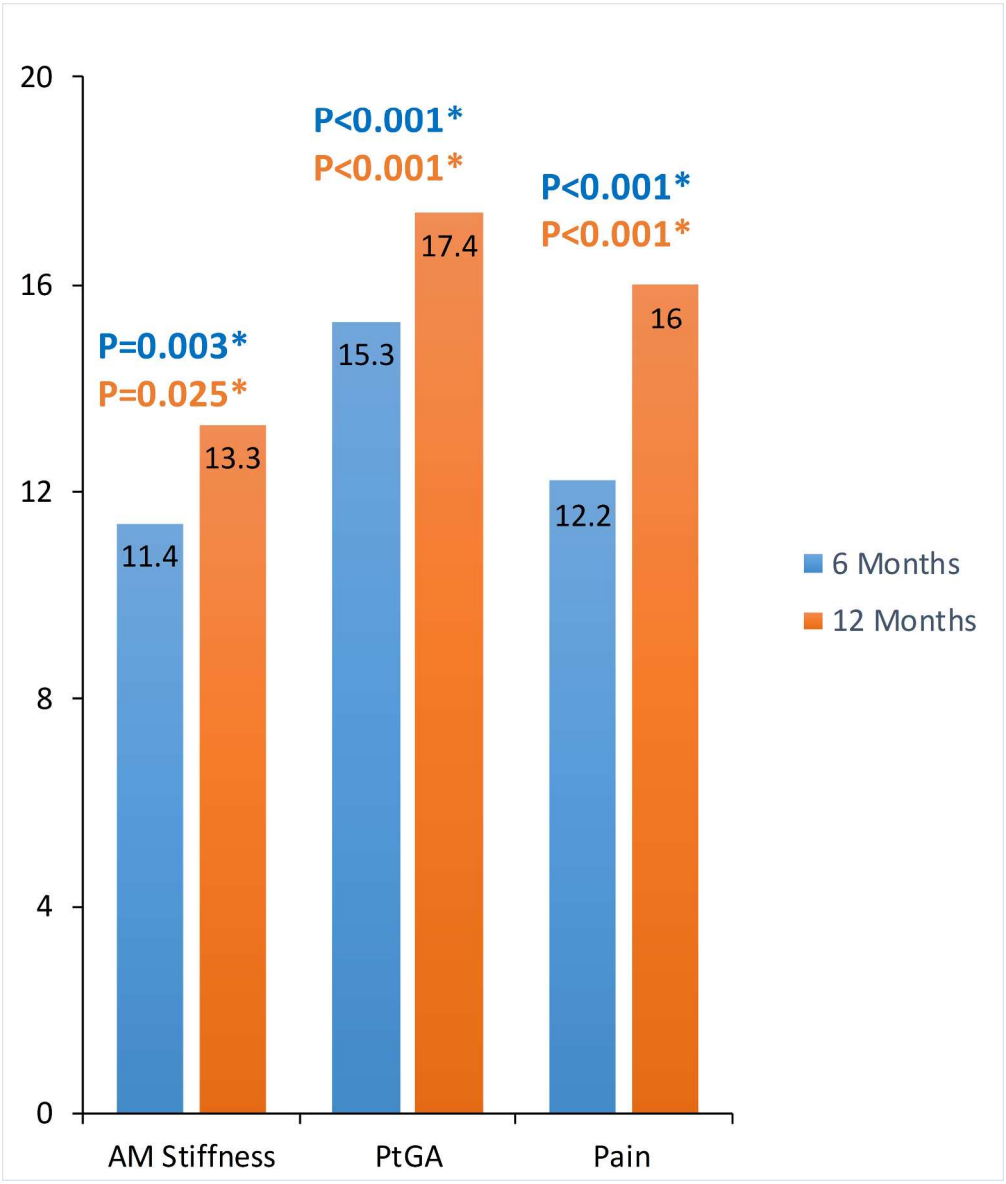

143x168mm (600 x 600 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6-7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 9 & Fig.1
		(b) Give reasons for non-participation at each stage	Fig.1
		(c) Consider use of a flow diagram	Fig.1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	8-9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-13
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18-19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Real World Validation of the Minimal Disease Activity Index in Psoriatic Arthritis: An Analysis from a Prospective, Observational, Biological Treatment Registry

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Real World Validation of the Minimal Disease Activity Index in Psoriatic Arthritis: An Analysis from a Prospective, Observational, Biological Treatment Registry

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Structured Abstract

Objectives: To describe the minimal disease activity (MDA) rate over time in psoriatic arthritis (PsA) patients receiving anti-TNF agents, evaluate prognostic factors of MDA achievement, and identify the most common unmet criteria among MDA achievers.

Design: Biologic Treatment Registry Across Canada (BioTRAC): ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis, ankylosing spondylitis, or PsA with Infliximab (IFX), Golimumab (GLM) or ustekinumab.

Setting: 46 primary-care Canadian rheumatology practices.

Participants: 223 PsA patients receiving IFX (enrolled since 2005) and GLM (enrolled since 2010) with available MDA information at baseline, 6 months, and/or 12 months.

Primary and secondary outcome measures: MDA was defined as ≥5 of the following criteria: Tender Joint Count (TJC)-28 ≤1, Swollen Joint Count (SJC)-28 ≤1, Psoriasis Area Severity Index (PASI) ≤1, or Body Surface Area ≤3, Pain (VAS) ≤15mm, Patient's global assessment (PtGA) (VAS) ≤20mm, HAQ ≤0.5, tender entheseal points ≤1. Independent prognostic factors of MDA achievement were assessed with multivariate logistic regression.

Results: MDA was achieved by 11.7% of patients at baseline, 43.5% at 6 months, 44.8% at 12 months, and 48.8% at either 6 or 12 months. Among MDA achievers at 6 months, 75.7% sustained MDA at 12 months. Lower baseline HAQ (OR=0.210; 95% CI: 0.099-0.447) and lower TJC28 (OR=0.880; 95% CI: 0.804-0.964), were significant prognostic factors of MDA achievement over 12 months of treatment. The most commonly unmet MDA criteria among MDA achievers was patient reported pain (25%), PtGA (15%) and PASI (12%).

Conclusions: Almost 50% of patients treated with IFX or GLM in routine clinical care achieve MDA within the first year of treatment. Lower baseline HAQ and lower TJC28, were identified as significant prognostic factors of MDA achievement. The most commonly unmet criteria in patients who achieved MDA were pain, PtGA and PASI.

Trial Registration: NCT00741793, "Biologic Treatment Registry Across Canada (BioTRAC)"

Strengths and limitations of this study:

- The limitations in the current study are that the peripheral joint activity was measured using the 28 tender/swollen joint count although the Outcome Measures in Rheumatology Clinical Trials (OMERACT) recommends the measure of 68 tender/66 swollen joint counts.
- Furthermore, although several approaches were used to assess disease activity, radiographic images are not collected in BioTRAC, therefore not allowing the examination of radiographic progression.
- There is also potential bias given the observational nature of the study, a bias that is avoided when using data from clinical trials.
- The strength of the study is that patients were seen in a real world setting by Canadian rheumatologists during routine clinical practice which enhances the generalizability of the results to the target population.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic systemic inflammatory musculoskeletal disease characterized by synovitis, axial disease, enthesitis, or dactylitis, and psoriasis. It is variably associated with other extra-articular manifestations that affects women and men equally.[1] PsA also affects up to 30 to 40% of patients with psoriasis.[2] Previously PsA was considered a mild disease; however, evidence from the last two decades has shown that it is frequently an erosive and deforming in 40 to 60% of patients who are diagnosed within the first few years.[3-5] Furthermore, similarly to other rheumatic diseases such as rheumatoid arthritis (RA), PsA has been associated with impaired physical function, reduced quality of life, and increased mortality,[6-8] with about 20% of patients eventually developing a highly destructive and disabling form of PsA.[9] Manifestations of PsA contribute to disease burden due to the negative effects on the patient's psychological and psychosocial functioning, dissatisfaction with the management of the disease and the negative impact on daily living activities.[10]

Over the years, major clinical improvements have been achieved in the outcome of inflammatory rheumatic diseases due to improved treatment availability and more commonly adopted early treatment algorithms including the treat to target strategy which has become the standard of care for newly diagnosed patients in RA.[11,12] Treatment therapies in PsA such as tumor necrosis factor α blockers (anti TNF α), have demonstrated a reduction in disease activity and radiographic progression of joint damage.[13-15] Although remission remains the ultimate treatment goal, the complexity of PsA makes it difficult to identify valid criteria that mark a state of remission or low disease activity that take into account all dimensions of the clinical manifestations of the disease. In the past decades, different scores were used to evaluate the disease severity of PsA such as the Disease Activity Score using 28 joints (DAS28) originally developed for RA assessment, as well as the Psoriatic Arthritis Disease Activity Score

(PASDAS), a weighted index comprising assessments of joints, function, acute-phase response, quality of life (QOL), and patient and physician global VAS scores, and the Composite Psoriatic Disease Activity Index (CPDAI) which takes into account the assessment of different domains such as peripheral arthritis, skin disease, spinal disease, dactylitis, and enthesitis. The minimal disease activity (MDA) was developed to take into account the heterogeneity seen and measure the disease activity of several clinical domains which is a more suitable outcome measure compared to DAS28 which does not take into consideration the full spectrum of disease manifestations.[16] These MDA criteria were validated in randomized controlled trials and observational studies demonstrating that patients who achieved MDA for a period of 12 months or more experienced a reduction in radiographic joint damage progression.[17,18] The tight control of inflammation in early psoriatic arthritis (TICOPA) trial was the first randomised, controlled trial, with a treat to target approach in PsA patients where the tight control group were reviewed every 4 weeks with escalation of treatment if MDA criteria wasn't met. Patients in the tight control group showed significant improvements in joint and skin disease activity, as well as benefits in function and QOL compared to the standard of care group.[19] However as far as we know, no real world evidence data on MDA are available in the literature.

The aim of the current study is to 1) describe the rate of MDA achievement over time, 2) evaluate prognostic factors of MDA achievement, 3) assess which unmet criteria were more common among patients who achieved MDA, 4) evaluate which unmet criteria were more common among patients who were near MDA achievers, and 5) assess DAS28 remission, DAS28 deep remission, and the level of agreement between MDA and DAS28 remission in PsA patients treated with infliximab or golimumab, in a routine clinical practice setting. The analysis was done using data from the Biologic Treatment Registry Across Canada (BioTRAC), an

ongoing, community based, Canada-wide, multi-centre, prospective, observational registry of patients with inflammatory arthritis.

METHODS

Study design

BioTRAC is an ongoing Canadian multi-centre, prospective, observational registry collecting real world clinical, laboratory, patient-centric, and safety data in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis patients treated with infliximab (IFX), golimumab (GLM), or ustekinumab as part of their routine care. The historical development of the registry has been described by Thorne et al.[20] To date there are over 100 rheumatology sites, participating, both in an institutional and private setting, with over 2100 patients enrolled in the programme across all indications. In accordance with the observational nature of the registry, there is no protocol-defined intervention in patient management. All clinical decisions and treatments are based on routine practice and the judgement of the treating physicians. Patients provided written informed consent prior to participation in the study. Ethics approval for participation in the BioTRAC program was obtained from the respective Research Ethics Boards (REB) of participating institutional sites and a Central Institutional Review Board (IRB Services, Ontario Canada) for private practice sites. BioTRAC is conducted according to the tenets of the Declaration of Helsinki.

Study population

Biologic-naïve patients or patients previously treated with one biologic who are eligible for treatment with infliximab, golimumab, or ustekinumab as per their respective Canadian Product Monograph are considered for inclusion in the registry. For the purpose of the current analysis, 223 patients with PsA treated with infliximab (enrolled since 2005) or with golimumab (enrolled

since 2010) were included from 46 primary care rheumatology practices across Canada. All efficacy analyses were observed and included all enrolled PsA patients who received at least one dose of IFX or GLM, and had at least one follow up assessment with available MDA data at 6 or 12 months. Figure 1 represents the flow chart of the patient population over time.

Data collection

The following clinical/laboratory parameters and patient reported outcomes (PROs) are collected as per routine care at baseline and at all follow up visits, with suggested assessments every six months given that this is within acceptable practice patterns for patients with active PsA: morning (AM) stiffness, swollen joint count (SJC28), tender joint count (TJC28), patient's (PtGA), and physician's (MDGA) global assessment of disease activity, health assessment questionnaire (HAQ), patient's assessment of pain, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

Statistical Analysis

Descriptive statistics included mean and standard deviations for continuous variables, and proportions for categorical variables. The absolute improvement in disease parameters at 6 and 12 months of treatment was assessed with the non-parametric Wilcoxon Signed Ranks test, while between group differences for continuous and categorical variables were assessed with the non-parametric Kruskal-Wallis test and the Pearson Chi-square test, respectively. The improvement in MDA achievement, DAS28 remission (<2.6), and DAS28 deep remission (<1.98) over time was assessed for statistical significance with the McNemar test. Independent prognostic factors of MDA achievement at 6 or 12 months of treatment were assessed with backward conditional logistic regression; covariates considered were: province, gender, age, baseline biologic agent, MDGA, PtGA, pain, HAQ, SJC28, TJC28, and enthesitis count with probability for stepwise entry and removal at the 0.05 and 0.10 level, respectively. MDA was defined as the fulfillment of

≥5 of the following criteria: TJC28≤1, SJC28≤1, PASI≤1, pain (VAS) ≤15 mm, PtGA (VAS) ≤20 mm, HAQ≤0.5, tender entheseal points ≤1.[18] Modified MDA (mMDA) was defined as having skin and swollen joints as mandatory criteria of the 5/7 criteria. Near MDA was defined as fulfillment of 4/7 criteria. Patients with missing information included gender (n=21), age (n=89), disease duration (n=76), while baseline parameters for DAS28 (n=49), MDGA (n=31), CRP (n=51), ESR (n=48), AM stiffness (n=34), and TJC28, SJC28, PtGA, HAQ, pain, PASI (all, n=27). Furthermore 12%, 30%, and 38% of patients had missing MDA at baseline, 6 and 12-month follow-up, respectively (see Figure 1). DAPSA was defined as the sum of TJC28, SJC28, CRP (mg/dl), PtGA (VAS 0-10) and pain (VAS 0-10). There was no imputation of missing data in the current analysis. Statistical analyses were conducted with SPSS 21.0 (SPSS Inc., Chicago, IL).

RESULTS

Table 1 summarizes the patient demographics and characteristics by region at baseline. There were 130 (58.3%) and 93 (41.7%) patients on GLM and IFX, respectively. Mean (SD) age and disease duration was 49.8 (11.1) and 5.4 (6.3) years, respectively, and 50% were males. Baseline disease parameters for DAS28, TJC, SJC, pain, PtGA, MDGA, morning stiffness, HAQ, CRP, and ESR were statistically comparable at baseline among Canadian regions. However significant differences between regional groups were observed at baseline for mean (SD) disease duration (p=0.002), enthesitis count [Western: 6.8 (3.3), Ontario: 4.6 (4.2), Quebec: 3.4 (2.1), Maritime: 5.8 (3.6); p=0.012], and PASI [Western: 3.8 (4.2), Ontario: 3.7 (5.4), Quebec: 1.4 (2.9), Maritime: 1.2 (1.5); p<0.001]. Furthermore, use of a previous biologic (p=0.017), previous DMARD (p=0.047), and previous corticosteroid (p=0.006) showed significant between group differences among regions (Table 1).

Table 1. Demographics and disease characteristics by region at baseline

Parameter	Western (N=18)	Ontario (N=111)	Quebec (N=63)	Maritimes (N=31)	p-value	Total (N=223)
Socio-demographics						
Gender, n (%) [a]						
Male	5 (38.5)	44 (43.1)	35 (58.3)	17 (63.0)	0.107	101 (50.0)
Female	8 (61.5)	58 (56.9)	25 (41.7)	10 (37.0)		101 (50.0)
Age (years), mean (SD)	50.7 (14.6)	49.7 (10.7)	51.0 (11.6)	46.5 (9.9)	0.393	49.8 (11.1)
Disease Parameters, mean (SD)						
Disease duration (years)	4.0 (4.6)	5.4 (6.2)	7.5 (7.4)	1.9 (2.0)	0.002	5.4 (6.3)
DAS28	4.3 (0.8)	4.4 (1.7)	4.2 (1.3)	4.3 (1.8)	0.928	4.3 (1.6)
TJC28	8.1 (6.4)	7.1 (6.7)	5.8 (5.0)	9.0 (9.2)	0.555	7.0 (6.7)
SJC28	4.1 (3.8)	4.6 (4.7)	5.2 (4.1)	5.0 (5.1)	0.549	4.8 (4.5)
MDGA (VAS cm)	6.0 (2.1)	5.1 (2.4)	5.5 (2.3)	4.6 (1.4)	0.062	5.2 (2.2)
PtGA (VAS mm)	54.5 (27.1)	52.0 (28.3)	49.5 (22.2)	46.0 (25.6)	0.662	50.5 (26.1)
AM stiffness[b] (min)	54.6 (49.2)	48.1 (47.6)	35.5 (39.8)	49.1 (43.3)	0.237	45.0 (45.0)
HAQ	1.3 (0.5)	1.1 (0.7)	1.1 (0.6)	1.0 (0.7)	0.263	1.1 (0.7)
Pain (VAS mm)	47.9 (23.0)	49.2 (27.5)	48.4 (23.0)	40.7 (23.6)	0.492	47.6 (25.4)
PASI	3.8 (4.2)	3.7 (5.4)	1.4 (2.9)	1.2 (1.5)	<0.001	2.6 (4.4)
Enthesitis count[c]	6.8 (3.3)	4.6 (4.2)	3.4 (2.1)	5.8 (3.6)	0.012	4.9 (3.5)
ESR (mm/h)	14.0 (15.3)	22.5 (22.9)	19.4 (16.4)	19.0 (22.3)	0.566	20.7 (20.7)
CRP (mg/L)	12.4 (13.6)	17.7 (36.9)	10.7 (14.2)	14.1 (27.6)	0.952	14.7 (29.1)
Medications, n (%)						
Baseline Biologic Agent						
GLM	8 (44.4)	69 (62.2)	39 (61.9)	14 (45.2)	0.200	130 (58.3)
IFX	10 (55.6)	42 (37.8)	24 (38.1)	17 (54.8)		93 (41.7)
Previous biologic	3 (21.4)	5 (5.3)	10 (17.2)	7 (24.1)	0.017	25 (12.8)
Previous DMARD	12 (85.7)	59 (62.1)	47 (81.0)	21 (72.4)	0.047	139 (70.9)

Previous corticosteroid	6 (42.9)	17 (17.9)	21 (36.2)	3 (10.3)	0.006	47 (24.0)
Concomitant DMARD	11 (78.6)	52 (54.7)	40 (69.0)	19 (65.5)	0.164	122 (62.2)
Concomitant Methotrexate	4 (28.6)	43 (45.3)	35 (60.3)	16 (55.2)	0.102	98 (50.0)
Concomitant corticosteroid use	1 (7.1)	10 (10.5)	7 (12.1)	2 (6.9)	0.868	20 (10.2)

[a]Percentages based on available data
[b]Capped at 120 minutes.
[c]Among patients with enthesitis.
DAS28, Disease Activity Score; HAQ, Health assessment questionnaire; MDGA, Physician Global Assessment of Disease Activity; PASI, Psoriasis Area and Severity Index; PtGA, Patient Global Assessment of Disease Activity; SJC, Swollen joint count; TJC, Tender joint count; GLM, golimumab; IFX, infliximab.

All disease parameters showed statistically significant improvement over time from baseline to month 6 and month 12 ($p<0.05$) (supplementary material).

Figure 2 describes achievement of MDA, mMDA, DAS28 remission, DAS28 deep remission, and DAPSA remission over time. At baseline, 6, and 12 months of treatment, 11.7%, 43.5%, and 44.8% of patients achieved MDA, respectively, while 48.8% achieved MDA at 6 or 12 months. Additionally, 34.6% (n=28/81) achieved MDA at both 6 and 12 months of treatment (overall sustained MDA). Patients achieving mMDA at baseline, 6 and 12 months was 7.1%, 37.7%, and 36.2%, respectively. DAS28 remission (<2.6) was achieved by 14.4%, 50.0%, and 48.8% of patients, DAS28 deep remission (<1.98) by 8.6%, 33.9%, and 28.6%, and DAPSA remission (≤4), by 6.4%, 23.3%, and 25.0% at baseline, 6 months, and 12 months of treatment, respectively (Figure 2). The improvement in MDA achievement, DAS28 remission, and DAS28 deep remission from baseline to 6 months and 12 months was statistically significant for all measures of disease activity ($p<0.05$). Table 2 depicts sensitivity, specificity, positive and negative predictive values between MDA or mMDA and DAS28 remission, DAS28 deep remission, as well as DAPSA remission. There was substantial agreement between MDA and DAS28 remission as well as MDA and DAPSA remission with a Kappa measure of agreement of 0.653 and 0.652, respectively (both $p<0.001$) while that between MDA and DAS28 deep

remission showed moderate agreement with 0.598 (p<0.001). Similar results were observed for the association of mMDA with the relevant outcome measures.

Table 2. Agreement between MDA or mMDA, with DAS28 and DAPSA

Diagnostic Criteria Definitions	DAS28 Remission (<2.6)	DAS28 Deep Remission (<1.98)	DAPSA Remission (≤4)
MDA			
Sensitivity	70.7%	82.1%	100.0%
Specificity	92.3%	85.7%	85.9%
Positive Predictive Value	82.1%	60.4%	56.3%
Negative Predictive Value	86.4%	94.7%	100.0%
Kappa agreement (K)	0.653	0.598	0.652
mMDA			
Sensitivity	57.7%	71.8%	87.0%
Specificity	94.8%	90.4%	89.9%
Positive Predictive Value	84.5%	66.7%	61.0%
Negative Predictive Value	81.9%	92.3%	97.5%
Kappa agreement (K)	0.570	0.605	0.655

Univariate analysis (Table 3A) showed that male gender (p= 0.031) and lower age (p=0.011) were significantly associated with MDA achievement at 6 or 12 months of treatment. Furthermore, significant between-region differences were observed for MDA achievement at 6 or 12 months of treatment (p=0.019). Ontario and Quebec patients had the highest MDA rates with 56.0% and 52.9%, respectively, while 36.4% and 14.3% of patients in Maritime and Western provinces reached MDA, respectively. In addition, significantly lower disease severity

was observed at baseline among MDA achievers for the following disease parameters: MDGA (p<0.001), PtGA (p<0.001), pain (p<0.001), HAQ (p<0.001), SJC28 (p=0.001), TJC28 (p<0.001), and enthesitis count (p=0.013). Multivariate logistic regression analysis (Table 3B) showed that lower baseline HAQ (OR=0.210, p<0.001) and lower TJC28 (OR=0.880, p=0.006) were significant prognostic factors of MDA achievement over 12 months of treatment, while parameters of lower enthesitis count (OR=0.838, p=0.069) and GLM as the biologic agent (OR=2.228, p=0.073) showed a trend towards statistical significance. Overall, similar results were obtained when assessing predictors of mMDA instead of MDA (data not shown).

Table 3A. Univariate Analysis for MDA Achievement at 6 or 12 Months of Treatment

Parameters	MDA achievement at 6 or 12 months		p-value[c]
	Yes	No	
Province, n (%)			
Western	2 (14.3)	12 (85.7)	0.019
Ontario	42 (56.0)	33 (44.0)	
Quebec	27 (52.9)	24 (47.1)	
Maritimes	8 (36.4)	14 (63.6)	
Gender, n (%)			
Male	45 (59.2)	31 (40.8)	0.031
Female	28 (40.6)	41 (59.4)	
Age, mean (SD)	46.6 (12.0)	51.6 (10.7)	0.011
MDGA (VAS cm)[a], mean (SD)	4.3 (2.4)	5.9 (2.0)	<0.001
PtGA (VAS mm)[a], mean (SD)	39.7 (24.7)	56.8 (24.9)	<0.001
Pain (VAS mm)[a], mean (SD)	35.6 (24.4)	55.1 (23.2)	<0.001
HAQ[a], mean (SD)	0.7 (0.6)	1.3 (0.6)	<0.001
SJC28[a], mean (SD)	3.4 (3.8)	5.4 (4.4)	0.001
TJC28[a], mean (SD)	3.8 (4.1)	8.8 (6.8)	<0.001
Enthesitis count[a,b], mean (SD)	0.7 (1.4)	2.0 (3.3)	0.013
Baseline biologic agent			
GLM	48 (53.9)	41 (46.1)	0.158

IFX	31 (42.5)	42 (57.5)

[a]Denotes disease parameters at baseline.
[b]Among all patients (with and without enthesitis).
[c]P-value was assessed with chi-square for categorical variables or with non-parametric Mann-Whitney U test for continuous variables.

Table 3B. Multivariate Analysis for MDA Achievement at 6 or 12 Months of Treatment

Parameters	Beta	Odds Ratio	95% Confidence Intervals for Odds Ratio		p-value
			Lower	Upper	
Baseline HAQ	-1.561	0.210	0.099	0.447	<0.001
Baseline TJC28	-0.128	0.880	0.804	0.964	0.006
Baseline enthesitis count	-0.177	0.838	0.692	1.014	0.069
Baseline biologic agent: GLM vs. IFX	0.801	2.228	0.929	5.343	0.073

Multivariate analysis was assessed with backward conditional logistic regression, covariates entered were: province, gender, age, baseline biologic agent, MDGA, PtGA, Pain, HAQ, SJC28, TJC28, and enthesitis count with probability for stepwise entry and removal at the 0.05 and 0.10 level, respectively.

Among the patients who achieved MDA at any time point, the highest proportion met all 7 MDA criteria with 45.8%, while 24.4% met 6/7 criteria, and 29.8% met 5/7 criteria (Figure 3A). The most commonly unmet criteria among these cases were patient-reported pain (with 25.2%), PtGA (with 15.3%), and PASI (with 12.2%) (Figure 3B). Additionally, among the 309 instances of non-MDA achievement, the proportion of cases that achieved near MDA was 16.5% (51/309). The most common reason for non-MDA in near-MDA cases was patient-reported pain (82.4%) followed by PtGA (68.6%), and HAQ (60.8%) (Figure 3C). Interestingly, 9 patients with available data that had reached MDA at 6 months were not in MDA state after 12 months. It was determined that the most common criteria not met in this group were: PtGA (88.9%), enthesitis count (66.7%), TJC (55.6%), and PASI (33.3%).

DISCUSSION

The current analysis is the first community-based Canadian study presenting a 12 month follow up of 223 prospectively followed patients with PsA from the BioTRAC registry. All measures of disease activity in the current study showed a statistical improvement over time ($p<0.05$).

Reported MDA achievement at 6 and 12 months of treatment was comparable with 43.5% and 44.8%, respectively. Among MDA achievers at 6 months, 75.7% (n=28/37) had sustained MDA at 12 months. The MDA achievement rate of approximately 45% is in line with the rates reported by Mease et al. despite the randomized controlled setting of this study.[21] However, our findings are lower in comparison with two recent studies which reported that 64% of the study population achieved MDA after 12 months of treatment with anti TNF α therapy [22,23]. A slightly higher proportion of patients (48.8%) achieved DAS28 remission at 12 months compared to MDA, while the rates of mMDA (36.2%), DAS28 deep remission (28.6%) and DAPSA remission (25.0%) were lower suggesting that the latter measures are more strict. However, the MDA had substantial agreement with DAS28 and DAPSA remission, whereas moderate agreement was observed with DAS28 deep remission. Thus, the current analysis suggests that MDA criteria may be a more powerful and discriminatory method to assess PsA than DAS28. The simplicity in calculating MDA and the lack of requirement for acute phase reactants at the time of visit as compared to the DAS28, makes the MDA a more desirable and practical tool to measure disease outcome in PsA.

Adjusted analysis of baseline variables showed that lower HAQ, lower TJC28, lower enthesitis count, and GLM as the biologic agent were considered independent prognostic factors of MDA achievement over 12 months of treatment. In addition to HAQ [24,25], previous studies have also identified shorter symptom duration, greater general well-being (global visual analogue

scale) [24], younger age, higher C-reactive protein (CRP), and lower BASFI as significant predictors of MDA, which however, were not confirmed in our study.[26] Moreover, other studies have shown that baseline lower HAQ, higher swollen joint count, and no previous use of anti TNF α therapy are also prognostic factors of remission at 12 months of treatment.[27,28]

The current results also showed that the most common limiting factors among patients who achieved MDA were including pain, PtGA, and PASI. Among patients who achieved near-MDA, the most commonly unmet criteria were pain, PtGA, and HAQ. These results highlight the difference in perception of disease activity by physicians and patients in the relative importance placed on specific disease aspects.

All disease parameters showed a statistically significant improvement at 6 months of treatment and were sustained over the 12-month period. In a prospective cohort study by Saber *et al*., statistically significant improvements in clinical outcome measures were also observed for TJC28, SJC28, CRP, and HAQ at 12 months in patients treated with anti TNF α therapy ($p<0.001$ for all), wherein statistical improvement was achieved within the first 3 months of treatment.[27]

The limitations of the current study are that the peripheral joint activity was measured using the 28 tender/swollen joint count although the Outcome Measures in Rheumatology Clinical Trials (OMERACT) recommends the measure of 68 tender/66 swollen joint counts.[16] However, simplified joint counts have been shown to be sufficiently sensitive to measure clinical response in PsA patients.[29] Furthermore, although several approaches were used to assess disease activity, radiographic images are not collected in BioTRAC, therefore not allowing the examination of radiographic progression. There is also potential bias given the observational nature of the study, a bias that is avoided when using data from clinical trials. The strength of the

study is that patients were seen in a real world setting by Canadian rheumatologists during routine clinical practice which enhances the generalizability of the results to the target population.

In conclusion, our results showed overall improvement in clinical parameters and disease activity in PsA patients treated with infliximab or golimumab during the 2 year follow up. By 6 and 12 months of treatment almost 50% of patients achieved MDA, and among achievers of MDA the most commonly unmet criteria were patient-reported pain, PtGA, and PASI. Furthermore, lower baseline HAQ and lower TJC at baseline, were identified as significant prognostic factors of MDA achievement. This study provides evidence supporting the validity of MDA in real world and its usefulness in patient management under routine clinical care.

FIGURE LEGENDS

Figure 2. MDA Achievement, mMDA Achievement, DAS28 Remission, DAS28 Deep Remission, and DAPSA Remission over Time

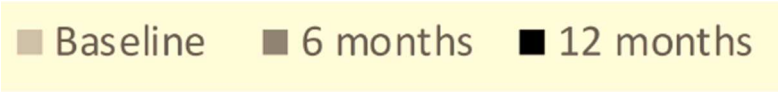
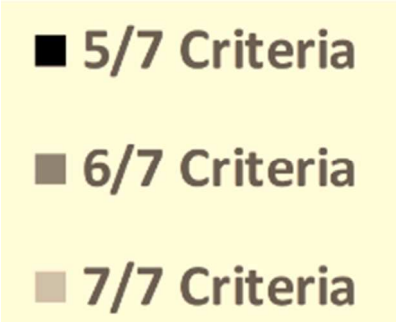


Figure 3A. Proportion of Met Criteria among MDA Achievers



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Competing interests:

Dr. Rahman reports personal fees from Janssen Inc., during the conduct of the study; personal fees from Abbott, AbbVie, Amgen, BMS, Celgene, Novartis, Pfizer, Roche, outside the submitted work. Dr. Zummer, Dr. Chow and Dr. Kapur report personal fees from Janssen Inc., during the conduct of the study. Dr. Bessette reports personal fees from Janssen Inc., during the conduct of the study; personal fees from Amgen, BMS, Roche, UCB, AbbVie, Pfizer, Merck, Sanofi, Celgene, Lilly, Novartis, outside the submitted work. Dr. Baer reports personal fees from Janssen Inc., during the conduct of the study; personal fees from AbbVie, Amgen, BMS, Pfizer, Roche, outside the submitted work. Dr. Haraoui reports personal fees from Janssen Inc., during the conduct of the study; personal fees from AbbVie, Amgen, BMS, Celgene, Pfizer, Roche, UCB, outside the submitted work. Dr. Kelsall reports personal fees from Janssen Inc., during the conduct of the study; personal fees from Abbott, AstraZeneca, BMS, Merck-Schering, Lilly, Pfizer, Wyeth, Roche, Takeda, UCB, outside the submitted work. Dr. Rampakakis and Ms. Psaradellis report personal fees from Janssen Inc. as employees of JSS Medical Research Inc., the CRO hired, during the conduct of the study. Dr. Lehman, Dr. Nantel, Dr. Osborne and Dr. Tkaczyk report personal fees as employees of Janssen Inc., during the conduct of the study.

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Contributorship statement:

Dr. Rahman, Dr. Zummer, Dr. Bessette, Dr. Baer, Dr. Haraoui, Dr. Chow, Dr. Kelsall and Dr. Kapur substantially contributed to the acquisition of the data for the work and revised the manuscript for important intellectual property. Dr. Rampakakis, Dr. Lehman, Dr. Nantel, Dr. Osborne and Dr. Tkaczyk substantially contributed to the conception or design of the work and the interpretation of the data for the work, and revised the manuscript critically for important intellectual content. Ms. Psaradellis substantially contributed to the analysis and interpretation of data for the work and drafted the manuscript. All authors approved the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Role of study sponsor: The sponsor, Janssen Inc., participated in the study design and interpretation of the data and funded all aspects of the study, but did not have an impact on data collection or the decision to submit the article for publication. The writing was conducted by a third party and the sponsor critically reviewed the manuscript.

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Access to data: All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Data sharing: No additional data available.

Checklist: The criteria described in the STROBE guidelines (checklist) have been satisfied.

What this paper adds:

What is already known on this subject:

- The control of disease activity adopting the treat-to-target strategy or minimal disease activity (MDA) has not been carefully established and is becoming the current challenge in management of PsA.
- As far as we know, there is no real-world evidence data on MDA available in the literature and our study will address this need.

What this study adds:

- The results of the current study showed that almost 50% of patients achieved MDA within the first year of treatment and thus provides evidence supporting the validity of

MDA in Canadian real-world and its usefulness in patient management under routine clinical care.

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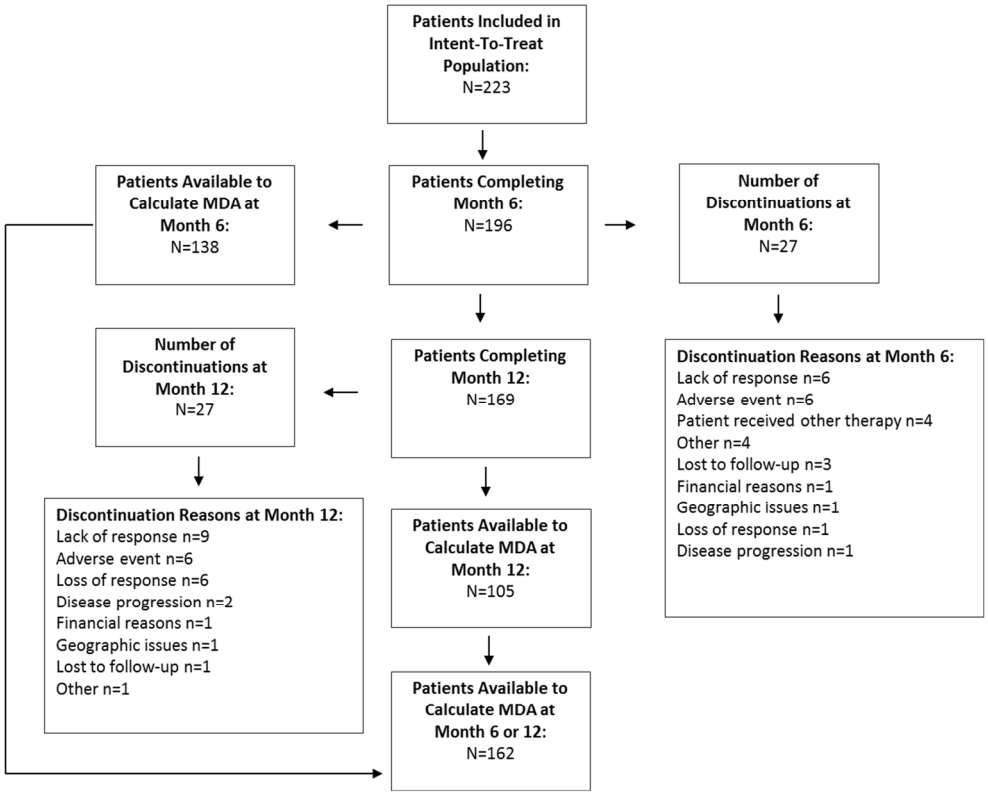

Flow chart of the patient population over time

90x72mm (600 x 600 DPI)

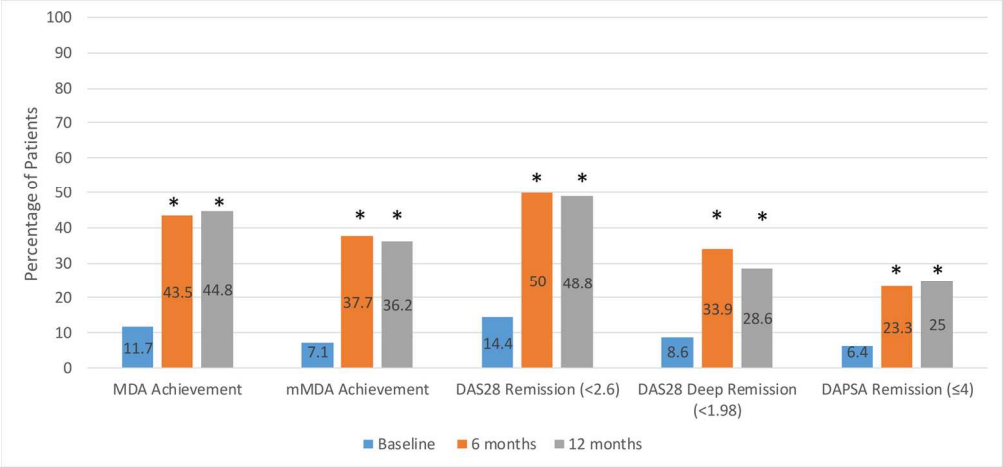

Figure 2. MDA Achievement, mMDA Achievement, DAS28 Remission, DAS28 Deep Remission, and DAPSA Remission over Time

*The improvement in MDA achievement, mMDA achievement, DAS28 remission, DAS28 deep remission and DAPSA remission from baseline to 6 months and from baseline to 12 months was assessed with the McNemar Test ($p<0.001$ for all, except DAS28 deep remission at 12 months $p=0.019$; and DAPSA remission at 12 months $p=0.006$).

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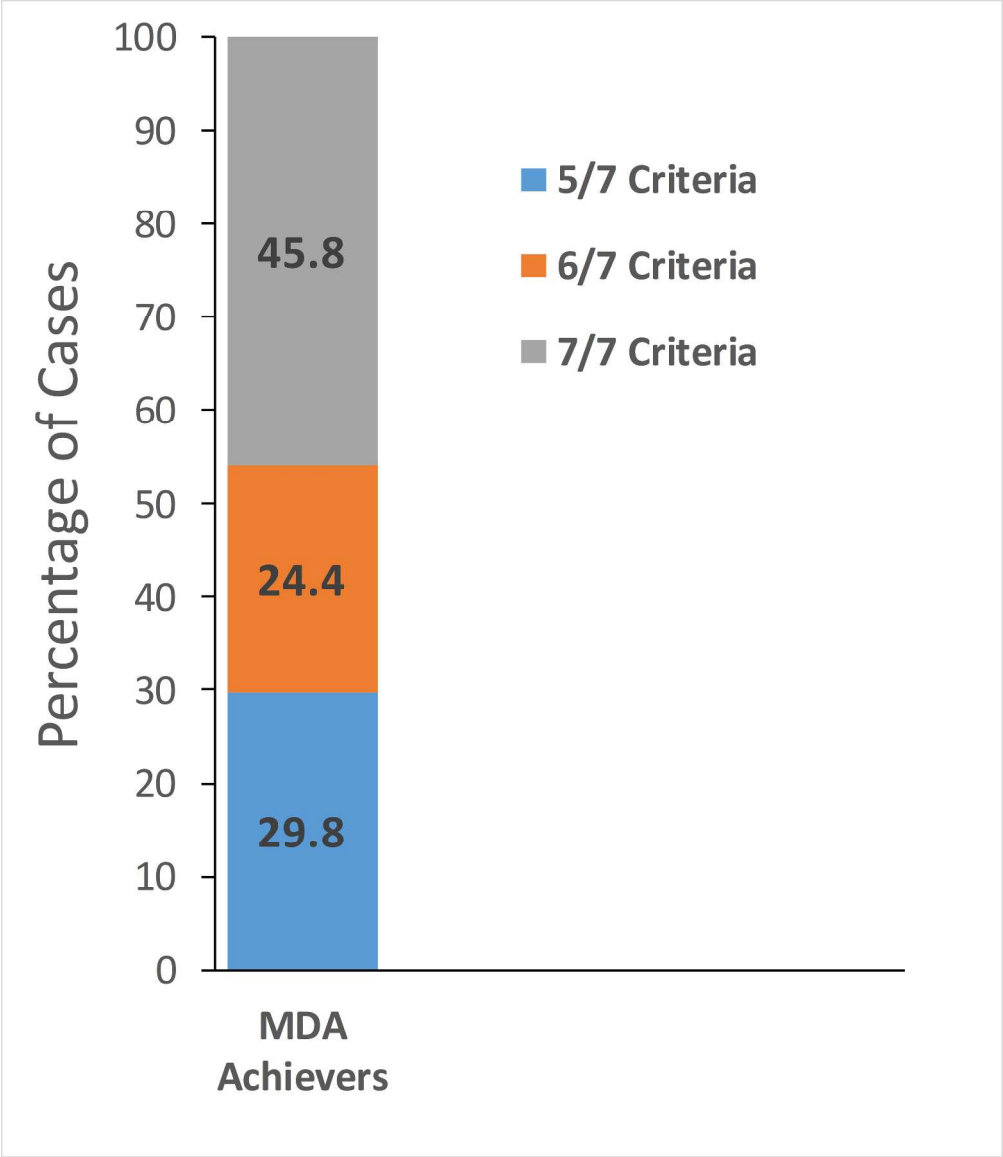
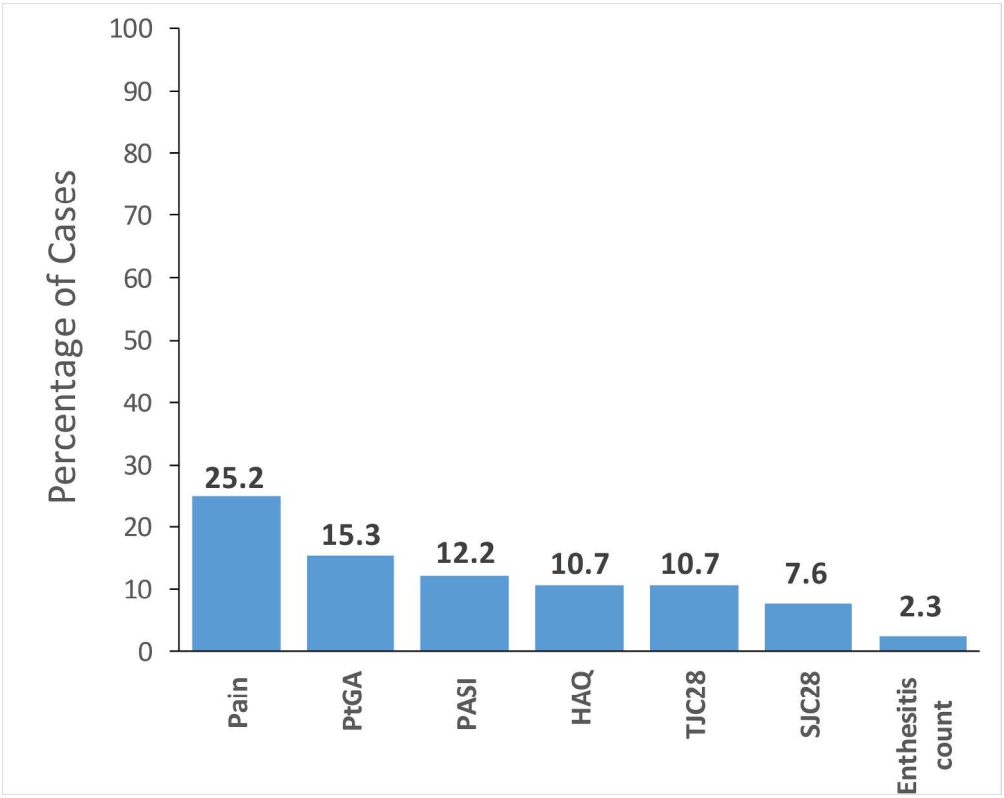


Proportion of Met Criteria among MDA Achievers

134x155mm (600 x 600 DPI)



Proportion of Unmet Disease Criteria among MDA Achievers

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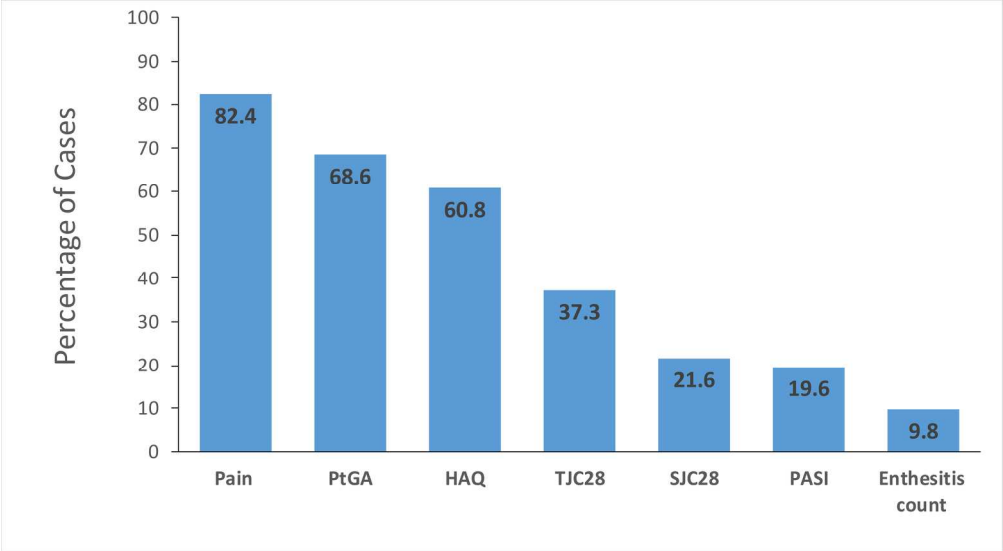

Proportion of Unmet Criteria among New MDA Achievers

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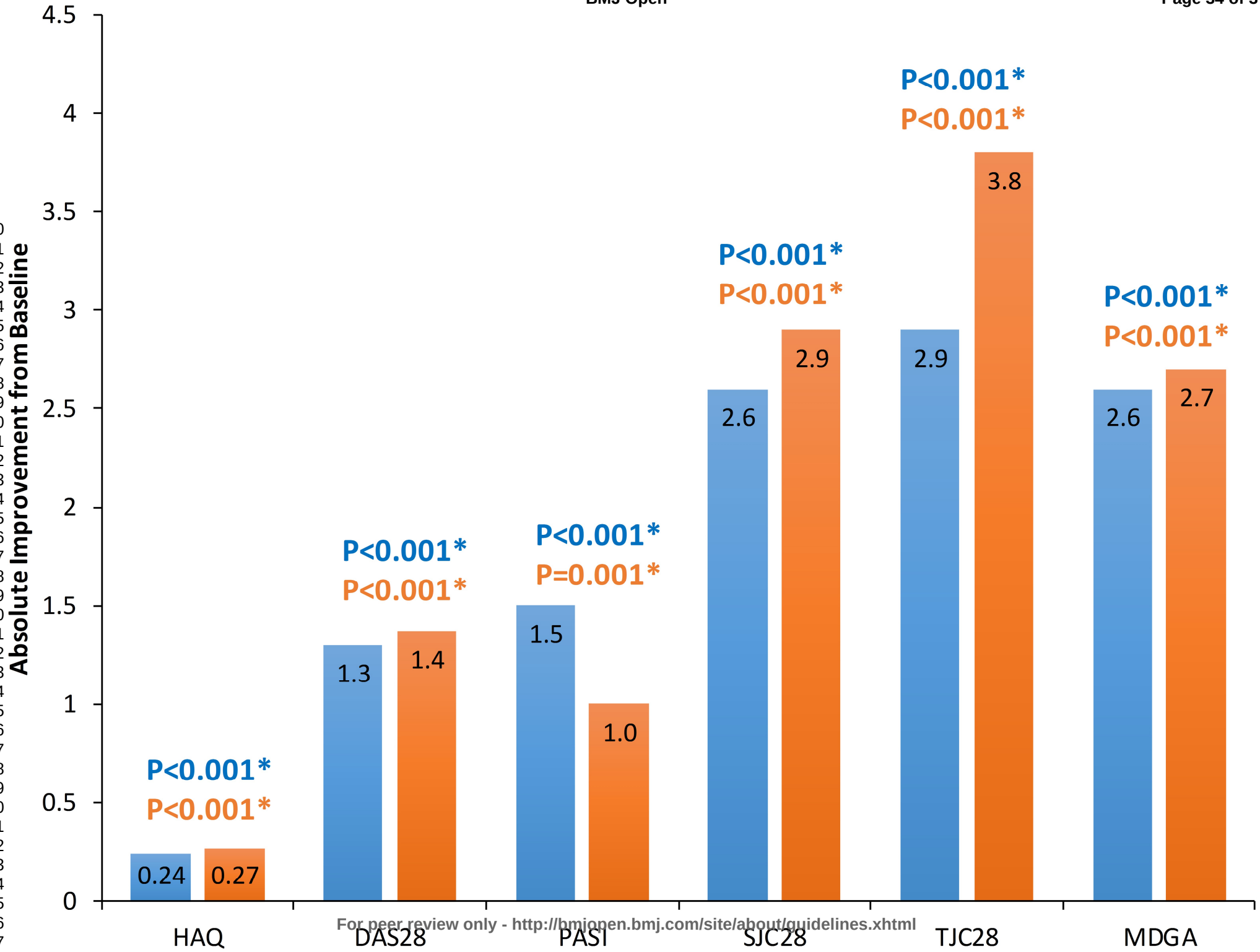

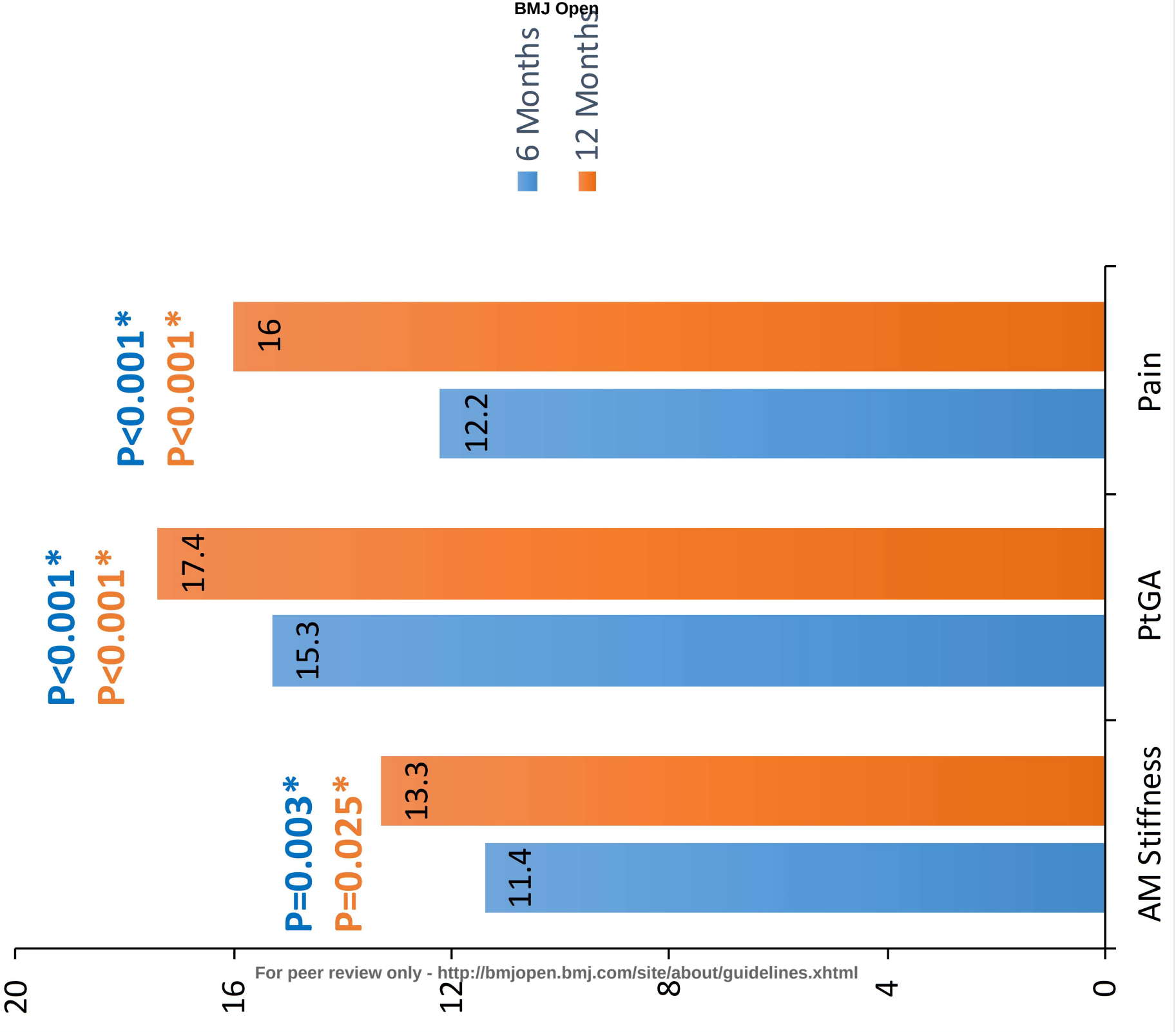

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6-7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 9 & Fig.1
		(b) Give reasons for non-participation at each stage	Fig.1
		(c) Consider use of a flow diagram	Fig.1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	8-9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-13
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18-19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Real World Validation of the Minimal Disease Activity Index in Psoriatic Arthritis: An Analysis from a Prospective, Observational, Biological Treatment Registry

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Real World Validation of the Minimal Disease Activity Index in Psoriatic Arthritis: An Analysis from a Prospective, Observational, Biological Treatment Registry

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Key words: Psoriatic arthritis, minimal disease activity, registry, real world, infliximab, golimumab

Structured Abstract

Objectives: To describe the minimal disease activity (MDA) rate over time in psoriatic arthritis (PsA) patients receiving anti-TNF agents, evaluate prognostic factors of MDA achievement, and identify the most common unmet criteria among MDA achievers.

Design: Biologic Treatment Registry Across Canada (BioTRAC): ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis, ankylosing spondylitis, or PsA with Infliximab (IFX), Golimumab (GLM) or ustekinumab.

Setting: 46 primary-care Canadian rheumatology practices.

Participants: 223 PsA patients receiving IFX (enrolled since 2005) and GLM (enrolled since 2010) with available MDA information at baseline, 6 months, and/or 12 months.

Primary and secondary outcome measures: MDA was defined as ≥5 of the following criteria: Tender Joint Count (TJC)-28 ≤1, Swollen Joint Count (SJC)-28 ≤1, Psoriasis Area Severity Index (PASI) ≤1, or Body Surface Area ≤3, Pain (VAS) ≤15mm, Patient's global assessment (PtGA) (VAS) ≤20mm, HAQ ≤0.5, tender entheseal points ≤1. Independent prognostic factors of MDA achievement were assessed with multivariate logistic regression.

Results: MDA was achieved by 11.7% of patients at baseline, 43.5% at 6 months, 44.8% at 12 months, and 48.8% at either 6 or 12 months. Among MDA achievers at 6 months, 75.7% sustained MDA at 12 months. Lower baseline HAQ (OR=0.210; 95% CI: 0.099-0.447) and lower TJC28 (OR=0.880; 95% CI: 0.804-0.964), were significant prognostic factors of MDA achievement over 12 months of treatment. The most commonly unmet MDA criteria among MDA achievers was patient reported pain (25%), PtGA (15%) and PASI (12%).

Conclusions: Almost 50% of patients treated with IFX or GLM in routine clinical care achieve MDA within the first year of treatment. Lower baseline HAQ and lower TJC28, were identified as significant prognostic factors of MDA achievement. The most commonly unmet criteria in patients who achieved MDA were pain, PtGA and PASI.

Trial Registration: NCT00741793, "Biologic Treatment Registry Across Canada (BioTRAC)"

Strengths and limitations of this study:

- The limitations in the current study are that the peripheral joint activity was measured using the 28 tender/swollen joint count although the Outcome Measures in Rheumatology Clinical Trials (OMERACT) recommends the measure of 68 tender/66 swollen joint counts.
- Furthermore, although several approaches were used to assess disease activity, radiographic images are not collected in BioTRAC, therefore not allowing the examination of radiographic progression.
- There is also potential bias given the observational nature of the study, a bias that is avoided when using data from clinical trials.
- The strength of the study is that patients were seen in a real world setting by Canadian rheumatologists during routine clinical practice which enhances the generalizability of the results to the target population.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic systemic inflammatory musculoskeletal disease characterized by synovitis, axial disease, enthesitis, or dactylitis, and psoriasis. It is variably associated with other extra-articular manifestations that affects women and men equally.[1] PsA also affects up to 30 to 40% of patients with psoriasis.[2] Previously PsA was considered a mild disease; however, evidence from the last two decades has shown that it is frequently an erosive and deforming in 40 to 60% of patients who are diagnosed within the first few years.[3-5] Furthermore, similarly to other rheumatic diseases such as rheumatoid arthritis (RA), PsA has been associated with impaired physical function, reduced quality of life, and increased mortality,[6-8] with about 20% of patients eventually developing a highly destructive and disabling form of PsA.[9] Manifestations of PsA contribute to disease burden due to the negative effects on the patient's psychological and psychosocial functioning, dissatisfaction with the management of the disease and the negative impact on daily living activities.[10]

Over the years, major clinical improvements have been achieved in the outcome of inflammatory rheumatic diseases due to improved treatment availability and more commonly adopted early treatment algorithms including the treat to target strategy which has become the standard of care for newly diagnosed patients in RA.[11,12] Treatment therapies in PsA such as tumor necrosis factor α blockers (anti TNF α), have demonstrated a reduction in disease activity and radiographic progression of joint damage.[13-15] Although remission remains the ultimate treatment goal, the complexity of PsA makes it difficult to identify valid criteria that mark a state of remission or low disease activity that take into account all dimensions of the clinical manifestations of the disease. In the past decades, different scores were used to evaluate the disease severity of PsA such as the Disease Activity Score using 28 joints (DAS28) originally developed for RA assessment, as well as the Psoriatic Arthritis Disease Activity Score

(PASDAS), a weighted index comprising assessments of joints, function, acute-phase response, quality of life (QOL), and patient and physician global VAS scores, and the Composite Psoriatic Disease Activity Index (CPDAI) which takes into account the assessment of different domains such as peripheral arthritis, skin disease, spinal disease, dactylitis, and enthesitis. The minimal disease activity (MDA) was developed to take into account the heterogeneity seen and measure the disease activity of several clinical domains which is a more suitable outcome measure compared to DAS28 which does not take into consideration the full spectrum of disease manifestations.[16] These MDA criteria were validated in randomized controlled trials and observational studies demonstrating that patients who achieved MDA for a period of 12 months or more experienced a reduction in radiographic joint damage progression.[17,18] The tight control of inflammation in early psoriatic arthritis (TICOPA) trial was the first randomised, controlled trial, with a treat to target approach in PsA patients where the tight control group were reviewed every 4 weeks with escalation of treatment if MDA criteria wasn't met. Patients in the tight control group showed significant improvements in joint and skin disease activity, as well as benefits in function and QOL compared to the standard of care group.[19] However as far as we know, no real world evidence data on MDA are available in the literature.

The aim of the current study is to 1) describe the rate of MDA achievement over time, 2) evaluate prognostic factors of MDA achievement, 3) assess which unmet criteria were more common among patients who achieved MDA, 4) evaluate which unmet criteria were more common among patients who were near MDA achievers, and 5) assess DAS28 remission, DAS28 deep remission, and the level of agreement between MDA and DAS28 remission in PsA patients treated with infliximab or golimumab, in a routine clinical practice setting. The analysis was done using data from the Biologic Treatment Registry Across Canada (BioTRAC), an

ongoing, community based, Canada-wide, multi-centre, prospective, observational registry of patients with inflammatory arthritis.

METHODS

Study design

BioTRAC is an ongoing Canadian multi-centre, prospective, observational registry collecting real world clinical, laboratory, patient-centric, and safety data in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis patients treated with infliximab (IFX), golimumab (GLM), or ustekinumab as part of their routine care. The historical development of the registry has been described by Thorne et al.[20] To date there are over 100 rheumatology sites, participating, both in an institutional and private setting, with over 2100 patients enrolled in the programme across all indications. In accordance with the observational nature of the registry, there is no protocol-defined intervention in patient management. All clinical decisions and treatments are based on routine practice and the judgement of the treating physicians. Patients provided written informed consent prior to participation in the study. Ethics approval for participation in the BioTRAC program was obtained from the respective Research Ethics Boards (REB) of participating institutional sites and a Central Institutional Review Board (IRB Services, Ontario Canada) for private practice sites. BioTRAC is conducted according to the tenets of the Declaration of Helsinki.

Study population

Biologic-naïve patients or patients previously treated with one biologic who are eligible for treatment with infliximab, golimumab, or ustekinumab as per their respective Canadian Product Monograph are considered for inclusion in the registry. For the purpose of the current analysis, 223 patients with PsA treated with infliximab (enrolled since 2005) or with golimumab (enrolled

since 2010) were included from 46 primary care rheumatology practices across Canada. All efficacy analyses were observed and included all enrolled PsA patients who received at least one dose of IFX or GLM, and had at least one follow up assessment with available MDA data at 6 or 12 months. Figure 1 represents the flow chart of the patient population over time.

Data collection

The following clinical/laboratory parameters and patient reported outcomes (PROs) are collected as per routine care at baseline and at all follow up visits, with suggested assessments every six months given that this is within acceptable practice patterns for patients with active PsA: morning (AM) stiffness, swollen joint count (SJC28), tender joint count (TJC28), patient's (PtGA), and physician's (MDGA) global assessment of disease activity, health assessment questionnaire (HAQ), patient's assessment of pain, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

Statistical Analysis

Descriptive statistics included mean and standard deviations for continuous variables, and proportions for categorical variables. The absolute improvement in disease parameters at 6 and 12 months of treatment was assessed with the non-parametric Wilcoxon Signed Ranks test, while between group differences for continuous and categorical variables were assessed with the non-parametric Kruskal-Wallis test and the Pearson Chi-square test, respectively. The improvement in MDA achievement, DAS28 remission (<2.6), and DAS28 deep remission (<1.98) over time was assessed for statistical significance with the McNemar test. Independent prognostic factors of MDA achievement at 6 or 12 months of treatment were assessed with backward conditional logistic regression; covariates considered were: province, gender, age, baseline biologic agent, MDGA, PtGA, pain, HAQ, SJC28, TJC28, and enthesitis count with probability for stepwise entry and removal at the 0.05 and 0.10 level, respectively. MDA was defined as the fulfillment of

≥5 of the following criteria: TJC28≤1, SJC28≤1, PASI≤1, pain (VAS) ≤15 mm, PtGA (VAS) ≤20 mm, HAQ≤0.5, tender entheseal points ≤1.[18] Modified MDA (mMDA) was defined as having skin and swollen joints as mandatory criteria of the 5/7 criteria. Near MDA was defined as fulfillment of 4/7 criteria. Patients with missing information included gender (n=21), age (n=89), disease duration (n=76), while baseline parameters for DAS28 (n=49), MDGA (n=31), CRP (n=51), ESR (n=48), AM stiffness (n=34), and TJC28, SJC28, PtGA, HAQ, pain, PASI (all, n=27). Furthermore 12%, 30%, and 38% of patients had missing MDA at baseline, 6 and 12-month follow-up, respectively (see Figure 1). DAPSA was defined as the sum of TJC28, SJC28, CRP (mg/dl), PtGA (VAS 0-10) and pain (VAS 0-10). There was no imputation of missing data in the current analysis. Statistical analyses were conducted with SPSS 21.0 (SPSS Inc., Chicago, IL).

RESULTS

Table 1 summarizes the patient demographics and characteristics by region at baseline. There were 130 (58.3%) and 93 (41.7%) patients on GLM and IFX, respectively. Mean (SD) age and disease duration was 49.8 (11.1) and 5.4 (6.3) years, respectively, and 45.3% were males. Baseline disease parameters for DAS28, TJC, SJC, pain, PtGA, MDGA, morning stiffness, HAQ, CRP, and ESR were statistically comparable at baseline among Canadian regions. However significant differences between regional groups were observed at baseline for mean (SD) disease duration (p=0.002), enthesitis count [Western: 6.8 (3.3), Ontario: 4.6 (4.2), Quebec: 3.4 (2.1), Maritime: 5.8 (3.6); p=0.012], and PASI [Western: 3.8 (4.2), Ontario: 3.7 (5.4), Quebec: 1.4 (2.9), Maritime: 1.2 (1.5); p<0.001]. Furthermore, use of a previous biologic (p=0.017), previous DMARD (p=0.047), previous corticosteroid (p=0.006) and concomitant

methotrexate use (p=0.031) showed significant between group differences among regions (Table 1).

Table 1. Demographics and disease characteristics by region at baseline

Parameter	Western (N=18)	Ontario (N=111)	Quebec (N=63)	Maritimes (N=31)	p-value	Total (N=223)
Socio-demographics						
Gender, n (%)						
Male	5 (27.8)	44 (39.6)	35 (55.6)	17 (54.8)	0.107	101 (45.3)
Female	8 (44.4)	58 (52.3)	25 (39.77)	10 (32.3)		101 (45.3)
Missing	5 (27.8)	9 (8.1)	3 (4.8)	4 (12.9)		21 (9.4)
Age (years), mean (SD)	50.7 (14.6)	49.7 (10.7)	51.0 (11.6)	46.5 (9.9)	0.393	49.8 (11.1)
Disease Parameters, mean (SD)						
Disease duration (years)	4.0 (4.6)	5.4 (6.2)	7.5 (7.4)	1.9 (2.0)	0.002	5.4 (6.3)
DAS28	4.3 (0.8)	4.4 (1.7)	4.2 (1.3)	4.3 (1.8)	0.928	4.3 (1.6)
TJC28	8.1 (6.4)	7.1 (6.7)	5.8 (5.0)	9.0 (9.2)	0.555	7.0 (6.7)
SJC28	4.1 (3.8)	4.6 (4.7)	5.2 (4.1)	5.0 (5.1)	0.549	4.8 (4.5)
MDGA (VAS cm)	6.0 (2.1)	5.1 (2.4)	5.5 (2.3)	4.6 (1.4)	0.062	5.2 (2.2)
PtGA (VAS mm)	54.5 (27.1)	52.0 (28.3)	49.5 (22.2)	46.0 (25.6)	0.662	50.5 (26.1)
AM stiffness[a] (min)	54.6 (49.2)	48.1 (47.6)	35.5 (39.8)	49.1 (43.3)	0.237	45.0 (45.0)
HAQ	1.3 (0.5)	1.1 (0.7)	1.1 (0.6)	1.0 (0.7)	0.263	1.1 (0.7)
Pain (VAS mm)	47.9 (23.0)	49.2 (27.5)	48.4 (23.0)	40.7 (23.6)	0.492	47.6 (25.4)
PASI	3.8 (4.2)	3.7 (5.4)	1.4 (2.9)	1.2 (1.5)	<0.001	2.6 (4.4)
Enthesitis count[b]	6.8 (3.3)	4.6 (4.2)	3.4 (2.1)	5.8 (3.6)	0.012	4.9 (3.5)
ESR (mm/h)	14.0 (15.3)	22.5 (22.9)	19.4 (16.4)	19.0 (22.3)	0.566	20.7 (20.7)
CRP (mg/L)	12.4 (13.6)	17.7 (36.9)	10.7 (14.2)	14.1 (27.6)	0.952	14.7 (29.1)
Medications, n (%)						
Baseline Biologic Agent						

GLM	8 (44.4)	69 (62.2)	39 (61.9)	14 (45.2)	0.200	130 (58.3)
IFX	10 (55.6)	42 (37.8)	24 (38.1)	17 (54.8)		93 (41.7)
Previous biologic	3 (16.7)	5 (4.5)	10 (15.9)	7 (22.6)	0.012	25 (11.2)
Previous DMARD	12 (66.7)	59 (53.2)	47 (74.6)	21 (67.7)	0.036	139 (62.3)
Previous corticosteroid	6 (33.3)	17 (15.3)	21 (33.3)	3 (9.7)	0.008	47 (21.1)
Concomitant DMARD	11 (61.1)	52 (46.8)	40 (63.5)	19 (61.3)	0.135	122 (54.7)
Concomitant Methotrexate	4 (22.2)	43 (38.7)	35 (55.6)	16 (51.6)	0.031	98 (43.9)
Concomitant corticosteroid use	1 (5.6)	10 (9.0)	7 (11.1)	2 (6.5)	0.837	20 (9.0)

[a]Capped at 120 minutes.
[b]Among patients with enthesitis.
DAS28, Disease Activity Score; HAQ, Health assessment questionnaire; MDGA, Physician Global Assessment of Disease Activity; PASI, Psoriasis Area and Severity Index; PtGA, Patient Global Assessment of Disease Activity; SJC, Swollen joint count; TJC, Tender joint count; GLM, golimumab; IFX, infliximab.

All disease parameters showed statistically significant improvement over time from baseline to month 6 and month 12 ($p<0.05$) (Supplementary Figure 1).

Figure 2 describes achievement of MDA, mMDA, DAS28 remission, DAS28 deep remission, and DAPSA remission over time. At baseline, 6, and 12 months of treatment, 11.7%, 43.5%, and 44.8% of patients achieved MDA, respectively, while 48.8% achieved MDA at 6 or 12 months. Additionally, 34.6% (n=28/81) achieved MDA at both 6 and 12 months of treatment (overall sustained MDA). Patients achieving mMDA at baseline, 6 and 12 months was 7.1%, 37.7%, and 36.2%, respectively. DAS28 remission (<2.6) was achieved by 14.4%, 50.0%, and 48.8% of patients, DAS28 deep remission (<1.98) by 8.6%, 33.9%, and 28.6%, and DAPSA remission (≤4), by 6.4%, 23.3%, and 25.0% at baseline, 6 months, and 12 months of treatment, respectively (Figure 2). The improvement in MDA achievement, DAS28 remission, and DAS28 deep remission from baseline to 6 months and 12 months was statistically significant for all measures of disease activity ($p<0.05$). Table 2 depicts sensitivity, specificity, positive and negative predictive values between MDA or mMDA and DAS28 remission, DAS28 deep remission, as well as DAPSA remission. There was substantial agreement between MDA and

DAS28 remission as well as MDA and DAPSA remission with a Kappa measure of agreement of 0.653 and 0.652, respectively (both p<0.001) while that between MDA and DAS28 deep remission showed moderate agreement with 0.598 (p<0.001). Similar results were observed for the association of mMDA with the relevant outcome measures.

Table 2. Agreement between MDA or mMDA, with DAS28 and DAPSA

Diagnostic Criteria Definitions	DAS28 Remission (<2.6)	DAS28 Deep Remission (<1.98)	DAPSA Remission (≤4)
MDA			
Sensitivity	70.7%	82.1%	100.0%
Specificity	92.3%	85.7%	85.9%
Positive Predictive Value	82.1%	60.4%	56.3%
Negative Predictive Value	86.4%	94.7%	100.0%
Kappa agreement (K)	0.653	0.598	0.652
mMDA			
Sensitivity	57.7%	71.8%	87.0%
Specificity	94.8%	90.4%	89.9%
Positive Predictive Value	84.5%	66.7%	61.0%
Negative Predictive Value	81.9%	92.3%	97.5%
Kappa agreement (K)	0.570	0.605	0.655

Univariate analysis (Table 3A) showed that male gender (p= 0.031) and lower age (p=0.011) were significantly associated with MDA achievement at 6 or 12 months of treatment. Furthermore, significant between-region differences were observed for MDA achievement at 6 or 12 months of treatment (p=0.019). Ontario and Quebec patients had the highest MDA rates

with 56.0% and 52.9%, respectively, while 36.4% and 14.3% of patients in Maritime and Western provinces reached MDA, respectively. In addition, significantly lower disease severity was observed at baseline among MDA achievers for the following disease parameters: MDGA ($p<0.001$), PtGA ($p<0.001$), pain ($p<0.001$), HAQ ($p<0.001$), SJC28 ($p=0.001$), TJC28 ($p<0.001$), and enthesitis count ($p=0.013$). Multivariate logistic regression analysis (Table 3B) showed that lower baseline HAQ (OR=0.210, $p<0.001$) and lower TJC28 (OR=0.880, $p=0.006$) were significant prognostic factors of MDA achievement over 12 months of treatment, while parameters of lower enthesitis count (OR=0.838, $p=0.069$) and GLM as the biologic agent (OR=2.228, $p=0.073$) showed a trend towards statistical significance. Overall, similar results were obtained when assessing predictors of mMDA instead of MDA (data not shown).

Table 3A. Univariate Analysis for MDA Achievement at 6 or 12 Months of Treatment

Parameters	MDA achievement at 6 or 12 months		p-value[c]
	Yes	No	
Province, n (%)			
Western	2 (14.3)	12 (85.7)	0.019
Ontario	42 (56.0)	33 (44.0)	
Quebec	27 (52.9)	24 (47.1)	
Maritimes	8 (36.4)	14 (63.6)	
Gender, n (%)			
Male	45 (59.2)	31 (40.8)	0.031
Female	28 (40.6)	41 (59.4)	
Age, mean (SD)	46.6 (12.0)	51.6 (10.7)	0.011
MDGA (VAS cm)[a], mean (SD)	4.3 (2.4)	5.9 (2.0)	<0.001
PtGA (VAS mm)[a], mean (SD)	39.7 (24.7)	56.8 (24.9)	<0.001
Pain (VAS mm)[a], mean (SD)	35.6 (24.4)	55.1 (23.2)	<0.001
HAQ[a], mean (SD)	0.7 (0.6)	1.3 (0.6)	<0.001
SJC28[a], mean (SD)	3.4 (3.8)	5.4 (4.4)	0.001

TJC28[a], mean (SD)	3.8 (4.1)	8.8 (6.8)	<0.001
Enthesitis count[a,b], mean (SD)	0.7 (1.4)	2.0 (3.3)	0.013
Baseline biologic agent			
GLM	48 (53.9)	41 (46.1)	0.158
IFX	31 (42.5)	42 (57.5)	

[a]Denotes disease parameters at baseline.
[b]Among all patients (with and without enthesitis).
[c]P-value was assessed with chi-square for categorical variables or with non-parametric Mann-Whitney U test for continuous variables.

Table 3B. Multivariate Analysis for MDA Achievement at 6 or 12 Months of Treatment

Parameters	Beta	Odds Ratio	95% Confidence Intervals for Odds Ratio		p-value
			Lower	Upper	
Baseline HAQ	-1.561	0.210	0.099	0.447	<0.001
Baseline TJC28	-0.128	0.880	0.804	0.964	0.006
Baseline enthesitis count	-0.177	0.838	0.692	1.014	0.069
Baseline biologic agent: GLM vs. IFX	0.801	2.228	0.929	5.343	0.073

Multivariate analysis was assessed with backward conditional logistic regression, covariates entered were: province, gender, age, baseline biologic agent, MDGA, PtGA, Pain, HAQ, SJC28, TJC28, and enthesitis count with probability for stepwise entry and removal at the 0.05 and 0.10 level, respectively.

Among the patients who achieved MDA at any time point, the highest proportion met all 7 MDA criteria with 45.8%, while 24.4% met 6/7 criteria, and 29.8% met 5/7 criteria (Figure 3A). The most commonly unmet criteria among these cases were patient-reported pain (with 25.2%), PtGA (with 15.3%), and PASI (with 12.2%) (Figure 3B). Additionally, among the 309 instances of non-MDA achievement, the proportion of cases that achieved near MDA was 16.5% (51/309). The most common reason for non-MDA in near-MDA cases was patient-reported pain (82.4%) followed by PtGA (68.6%), and HAQ (60.8%) (Figure 3C). Interestingly, 9 patients with available data that had reached MDA at 6 months were not in MDA state after 12 months. It was

determined that the most common criteria not met in this group were: PtGA (88.9%), enthesitis count (66.7%), TJC (55.6%), and PASI (33.3%).

DISCUSSION

The current analysis is the first community-based Canadian study presenting a 12 month follow up of 223 prospectively followed patients with PsA from the BioTRAC registry. All measures of disease activity in the current study showed a statistical improvement over time ($p<0.05$).

Reported MDA achievement at 6 and 12 months of treatment was comparable with 43.5% and 44.8%, respectively. Among MDA achievers at 6 months, 75.7% (n=28/37) had sustained MDA at 12 months. The MDA achievement rate of approximately 45% is in line with the rates reported by Mease et al. despite the randomized controlled setting of this study.[21] However, our findings are lower in comparison with two recent studies which reported that 64% of the study population achieved MDA after 12 months of treatment with anti TNF α therapy [22,23]. A slightly higher proportion of patients (48.8%) achieved DAS28 remission at 12 months compared to MDA, while the rates of mMDA (36.2%), DAS28 deep remission (28.6%) and DAPSA remission (25.0%) were lower suggesting that the latter measures are more strict. However, the MDA had substantial agreement with DAS28 and DAPSA remission, whereas moderate agreement was observed with DAS28 deep remission. Thus, the current analysis suggests that MDA criteria may be a more powerful and discriminatory method to assess PsA than DAS28. The simplicity in calculating MDA and the lack of requirement for acute phase reactants at the time of visit as compared to the DAS28, makes the MDA a more desirable and practical tool to measure disease outcome in PsA.

Adjusted analysis of baseline variables showed that lower HAQ, lower TJC28, lower enthesitis count, and GLM as the biologic agent were considered independent prognostic factors of MDA achievement over 12 months of treatment. In addition to HAQ [24,25], previous studies have also identified shorter symptom duration, greater general well-being (global visual analogue scale) [24], younger age, higher C-reactive protein (CRP), and lower BASFI as significant predictors of MDA, which however, were not confirmed in our study.[26] Moreover, other studies have shown that baseline lower HAQ, higher swollen joint count, and no previous use of anti TNF α therapy are also prognostic factors of remission at 12 months of treatment.[27,28]

The current results also showed that the most common limiting factors among patients who achieved MDA were including pain, PtGA, and PASI. Among patients who achieved near-MDA, the most commonly unmet criteria were pain, PtGA, and HAQ. These results highlight the difference in perception of disease activity by physicians and patients in the relative importance placed on specific disease aspects.

All disease parameters showed a statistically significant improvement at 6 months of treatment and were sustained over the 12-month period. In a prospective cohort study by Saber *et al*., statistically significant improvements in clinical outcome measures were also observed for TJC28, SJC28, CRP, and HAQ at 12 months in patients treated with anti TNF α therapy ($p<0.001$ for all), wherein statistical improvement was achieved within the first 3 months of treatment.[27]

The limitations of the current study are that the peripheral joint activity was measured using the 28 tender/swollen joint count although the Outcome Measures in Rheumatology Clinical Trials (OMERACT) recommends the measure of 68 tender/66 swollen joint counts.[16] However, simplified joint counts have been shown to be sufficiently sensitive to measure clinical response

in PsA patients.[29] Furthermore, although several approaches were used to assess disease activity, radiographic images are not collected in BioTRAC, therefore not allowing the examination of radiographic progression. There is also potential bias given the observational nature of the study, a bias that is avoided when using data from clinical trials. In addition, a considerable number of patients did not have available MDA information at follow-up due to incomplete data, therefore there is risk for selection bias. In a drop-out analysis no statistical differences were observed between patients with and without MDA information, however, the latter had numerically higher TJC (8.0 vs 6.4) and enthesitis count (5.4 vs. 4.5). Furthermore, given that patients treated with either IFX or GLM were included and the profile of patients selected for each treatment may differ, there is risk for confounding by indication. However, the comparison of the two treatments was not within the scope of the current analysis and adjusted estimates were produced for MDA achievement. The strength of the study is that patients were seen in a real world setting by Canadian rheumatologists during routine clinical practice which enhances the generalizability of the results to the target population.

In conclusion, our results showed overall improvement in clinical parameters and disease activity in PsA patients treated with infliximab or golimumab during the 2 year follow up. By 6 and 12 months of treatment almost 50% of patients achieved MDA, and among achievers of MDA the most commonly unmet criteria were patient-reported pain, PtGA, and PASI. Furthermore, lower baseline HAQ and lower TJC at baseline, were identified as significant prognostic factors of MDA achievement. This study provides evidence supporting the validity of MDA in real world and its usefulness in patient management under routine clinical care.

Acknowledgments: Not applicable

Competing interests:

Dr. Rahman reports personal fees from Janssen Inc., during the conduct of the study; personal fees from Abbott, AbbVie, Amgen, BMS, Celgene, Novartis, Pfizer, Roche, outside the submitted work. Dr. Zummer, Dr. Chow and Dr. Kapur report personal fees from Janssen Inc., during the conduct of the study. Dr. Bessette reports personal fees from Janssen Inc., during the conduct of the study; personal fees from Amgen, BMS, Roche, UCB, AbbVie, Pfizer, Merck, Sanofi, Celgene, Lilly, Novartis, outside the submitted work. Dr. Baer reports personal fees from Janssen Inc., during the conduct of the study; personal fees from AbbVie, Amgen, BMS, Pfizer, Roche, outside the submitted work. Dr. Haraoui reports personal fees from Janssen Inc., during the conduct of the study; personal fees from AbbVie, Amgen, BMS, Celgene, Pfizer, Roche, UCB, outside the submitted work. Dr. Kelsall reports personal fees from Janssen Inc., during the conduct of the study; personal fees from Abbott, AstraZeneca, BMS, Merck-Schering, Lilly, Pfizer, Wyeth, Roche, Takeda, UCB, outside the submitted work. Dr. Rampakakis and Ms. Psaradellis report personal fees from Janssen Inc. as employees of JSS Medical Research Inc., the CRO hired, during the conduct of the study. Dr. Lehman, Dr. Nantel, Dr. Osborne and Dr. Tkaczyk report personal fees as employees of Janssen Inc., during the conduct of the study.

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Contributorship statement:

Dr. Rahman, Dr. Zummer, Dr. Bessette, Dr. Baer, Dr. Haraoui, Dr. Chow, Dr. Kelsall and Dr. Kapur substantially contributed to the acquisition of the data for the work and revised the manuscript for important intellectual property. Dr. Rampakakis, Dr. Lehman, Dr. Nantel, Dr. Osborne and Dr. Tkaczyk substantially contributed to the conception or design of the work and the interpretation of the data for the work, and revised the manuscript critically for important intellectual content. Ms. Psaradellis substantially contributed to the analysis and interpretation of data for the work and drafted the manuscript. All authors approved the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Role of study sponsor: The sponsor, Janssen Inc., participated in the study design and interpretation of the data and funded all aspects of the study, but did not have an impact on data collection or the decision to submit the article for publication. The writing was conducted by a third party and the sponsor critically reviewed the manuscript.

Independence: The study researchers were independent from funders.

Access to data: All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; any discrepancies from the study as planned have been explained.

Data sharing: No additional data available.

Checklist: The criteria described in the STROBE guidelines (checklist) have been satisfied.

What this paper adds:

What is already known on this subject:

- The control of disease activity adopting the treat-to-target strategy or minimal disease activity (MDA) has not been carefully established and is becoming the current challenge in management of PsA.
- As far as we know, there is no real-world evidence data on MDA available in the literature and our study will address this need.

What this study adds:

- The results of the current study showed that almost 50% of patients achieved MDA within the first year of treatment and thus provides evidence supporting the validity of

MDA in Canadian real-world and its usefulness in patient management under routine clinical care.

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FIGURE LEGENDS

Figure 1. Flow Chart of the Patient Population over Time

Legend: not applicable

Figure 2. MDA Achievement, mMDA Achievement, DAS28 Remission, DAS28 Deep Remission, and DAPSA Remission over Time

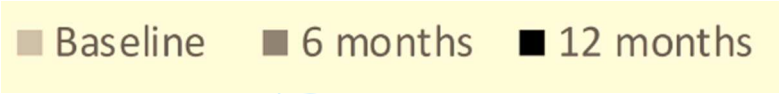


Figure 3A. Proportion of Met Criteria among MDA Achievers

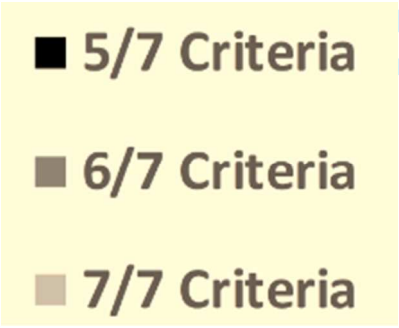


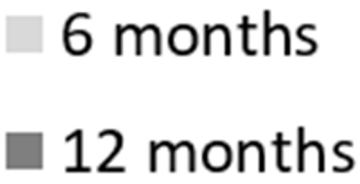
Figure 3B. Proportion of Unmet Disease Criteria among MDA Achievers

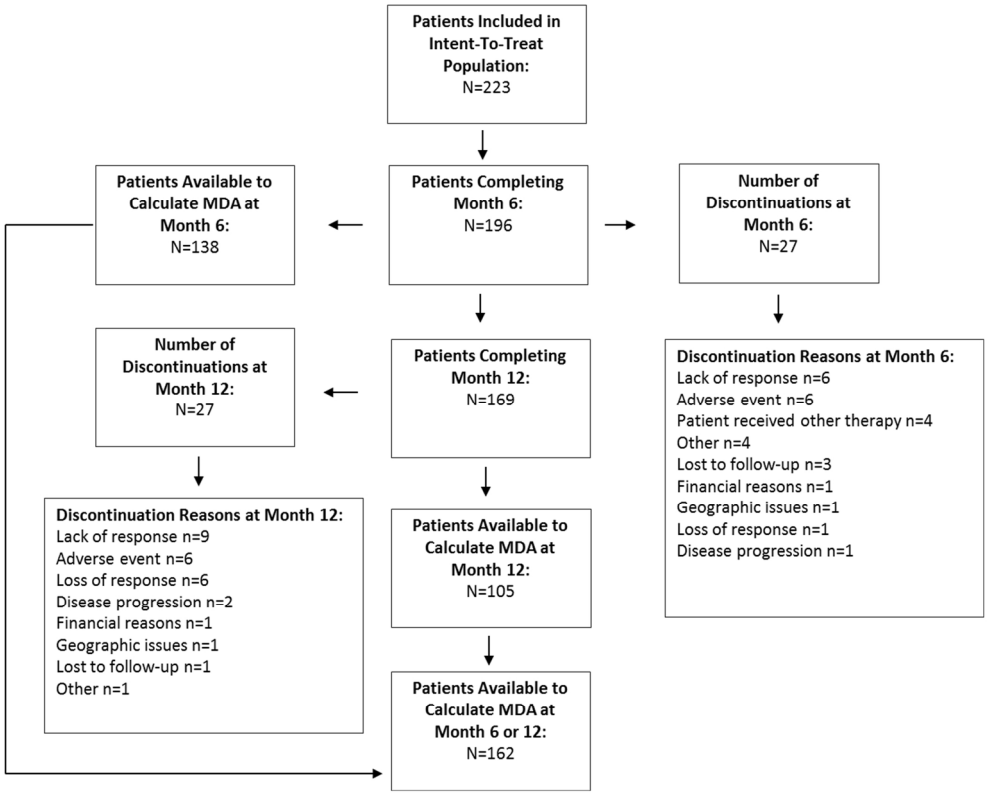
Legend: not applicable

Figure 3C: Proportion of Umet Criteria among New MDA Achievers

Legend: not applicable

Supplementary Figure 1: Improvement in Disease Parameters at 6 and 12 Months





Flow chart of the patient population over time

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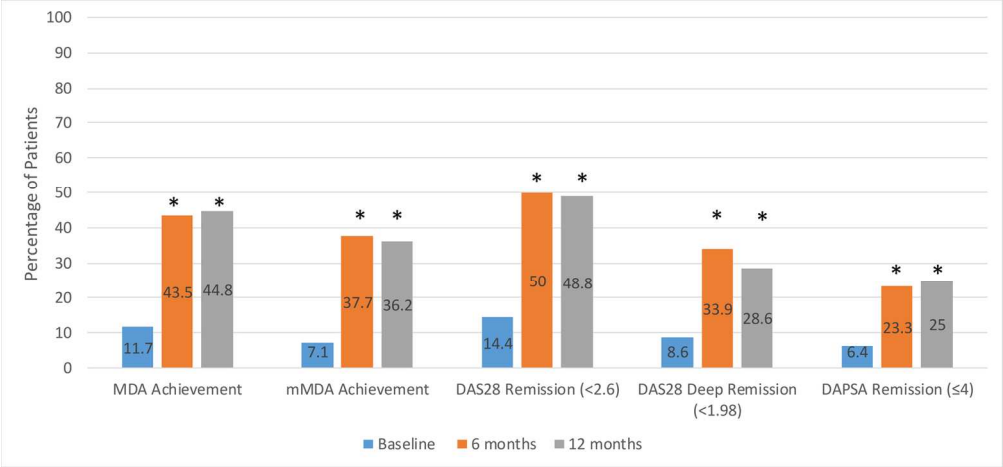

Figure 2. MDA Achievement, mMDA Achievement, DAS28 Remission, DAS28 Deep Remission, and DAPSA Remission over Time

*The improvement in MDA achievement, mMDA achievement, DAS28 remission, DAS28 deep remission and DAPSA remission from baseline to 6 months and from baseline to 12 months was assessed with the McNemar Test ($p<0.001$ for all, except DAS28 deep remission at 12 months $p=0.019$; and DAPSA remission at 12 months $p=0.006$).

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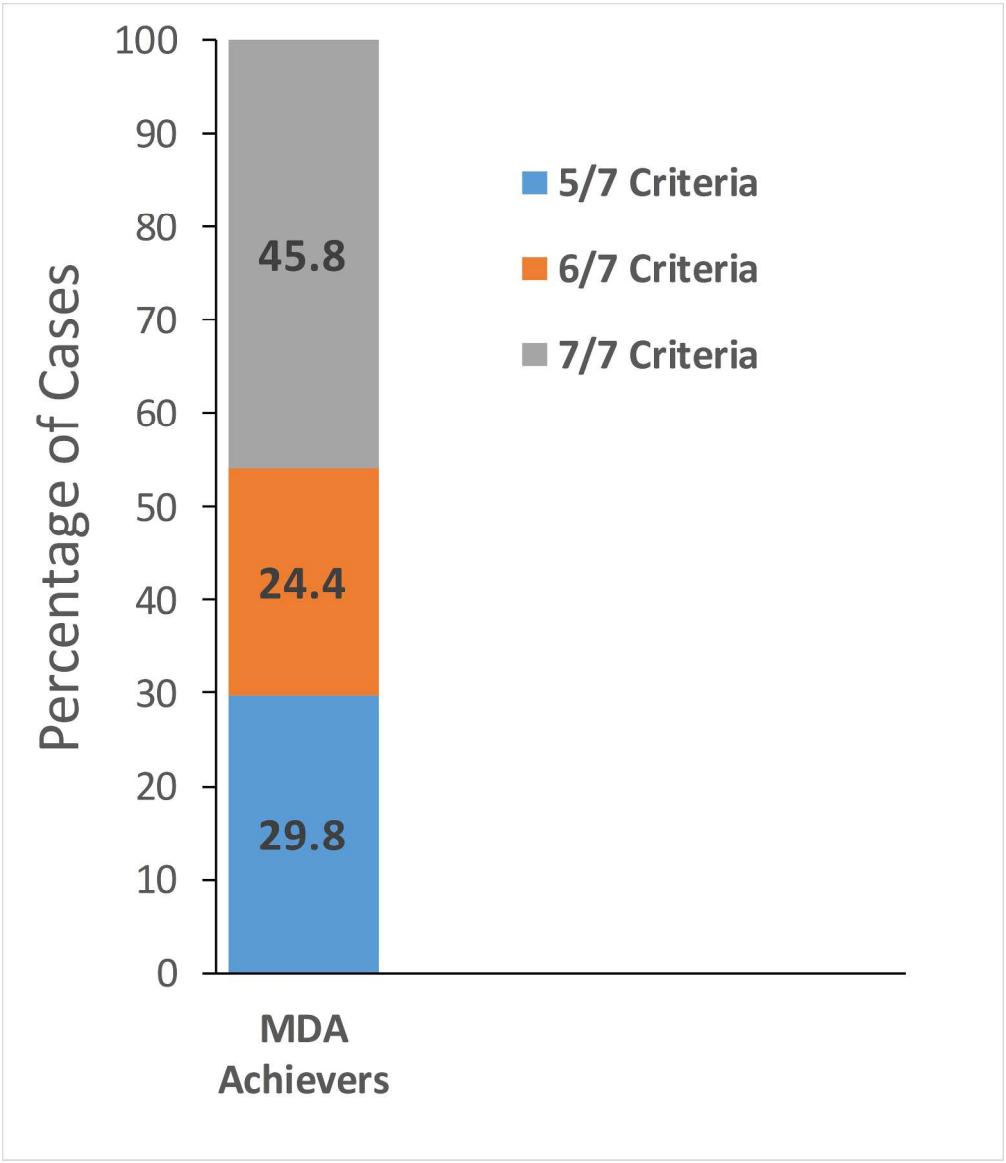

Proportion of Met Criteria among MDA Achievers

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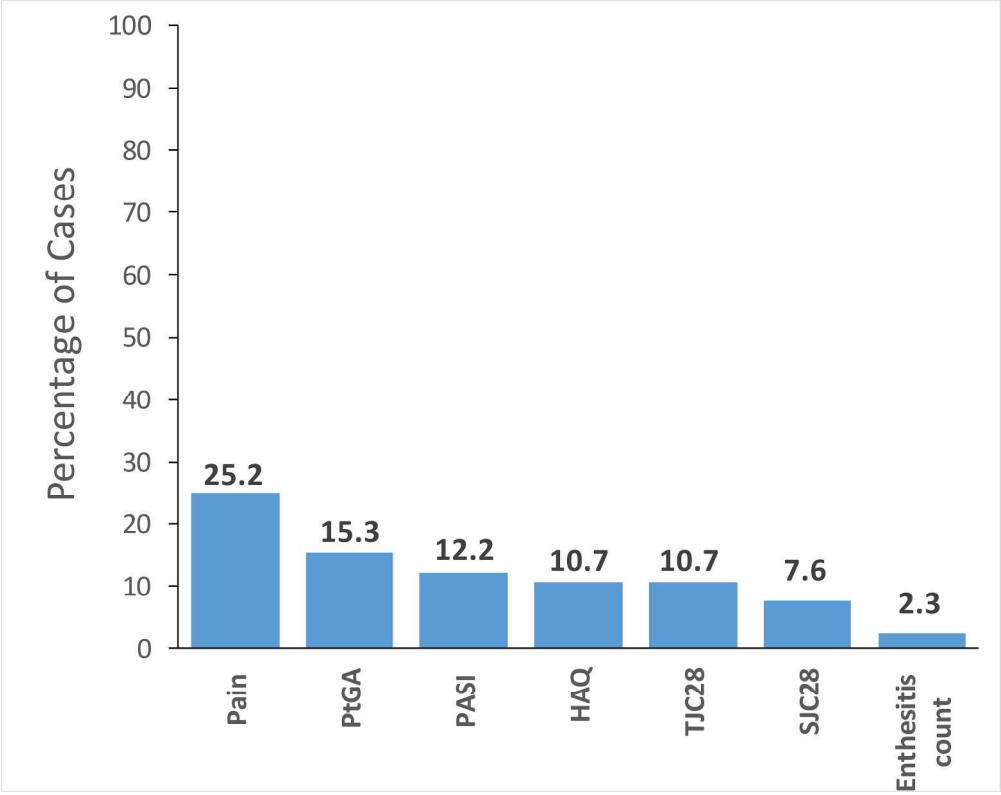

Proportion of Unmet Disease Criteria among MDA Achievers

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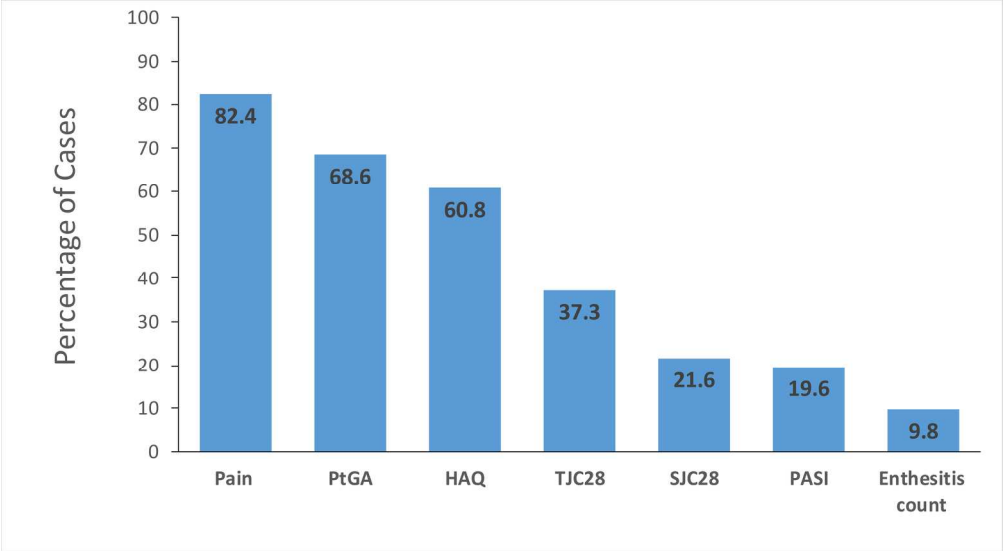

Proportion of Unmet Criteria among New MDA Achievers

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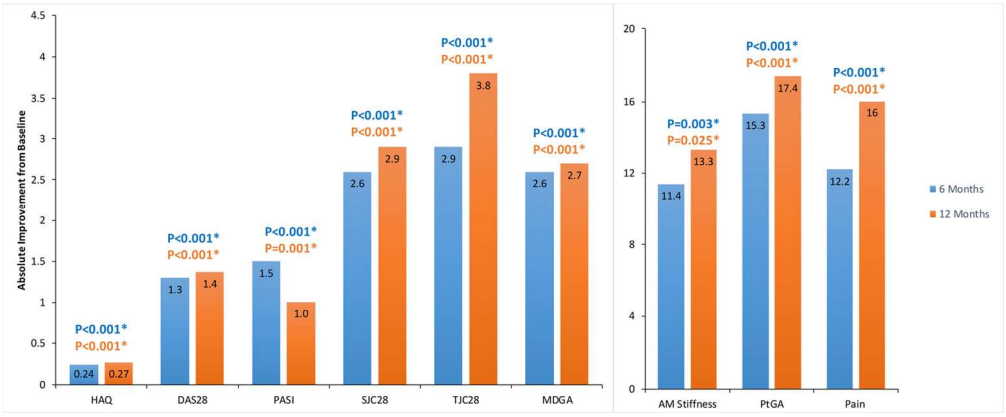

Improvement in Disease Parameters at 6 and 12 Months

71x29mm (600 x 600 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6-7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 9 & Fig.1
		(b) Give reasons for non-participation at each stage	Fig.1
		(c) Consider use of a flow diagram	Fig.1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	8-9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-13
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18-19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.