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TOFA-PREDICT study protocol: a stratification trial to determine key immunological factors predicting tofacitinib efficacy and drug-free remission in psoriatic arthritis (PsA)

Nienke J Kleinrensink,[1,2] Frank T Perton ,[1] Juliëtte N Pouw ,[1,3] Nanette L A Vincken ,[1,3] Sarita A Y Hartgring,[1,3] Mylène P Jansen ,[1] Saeed Arbabi,[4,5] TOFA-PREDICT author group, Wouter Foppen ,[2] Pim A de Jong,[2] Janneke Tekstra,[1] Emmerik F A Leijten,[1,3] Julia Spierings ,[1] Floris P J G Lafeber,[1] Paco M J Welsing,[1] Marloes W Heijstek[1]

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NJK, FTP, JNP and NLAV contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Frank T Perton;
f.perton@umcutrecht.nl

ABSTRACT

Introduction Psoriatic arthritis (PsA) is a chronic, inflammatory, musculoskeletal disease that affects up to 30% of patients with psoriasis. Current challenges in clinical care and research include personalised treatment, understanding the divergence of therapy response and unravelling the multifactorial pathophysiology of this complex disease. Moreover, there is an urgent clinical need to predict, assess and understand the cellular and molecular pathways underlying the response to disease-modifying antirheumatic drugs (DMARDs). The TOFA-PREDICT clinical trial addresses this need. Our primary objective is to determine key immunological factors predicting tofacitinib efficacy and drug-free remission in PsA.

Methods and analysis In this investigator-initiated, phase III, multicentre, open-label, four-arm randomised controlled trial, we plan to integrate clinical, molecular and imaging parameters of 160 patients with PsA. DMARD-naïve patients are randomised to methotrexate or tofacitinib. Additionally, patients who are non-responsive to conventional synthetic (cs)DMARDs continue their current csDMARD and are randomised to etanercept or tofacitinib. This results in four arms each with 40 patients. Patients are followed for 1 year. Treatment response is defined as minimal disease activity at week 16. Clinical data, biosamples and images are collected at baseline, 4 weeks and 16 weeks; at treatment failure (treatment switch) and 52 weeks. For the first 80 patients, we will use a systems medicine approach to assess multiomics biomarkers and develop a prediction model for treatment response. Subsequently, data from the second 80 patients will be used for validation.

Ethics and dissemination The study was approved by the Medical Research Ethics Committee in Utrecht, Netherlands, is registered in the European Clinical Trials Database and is carried out in accordance with the Declaration of Helsinki. The study's progress is monitored by Julius Clinical, a science-driven contract research organisation.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our multiomics systems medicine approach integrates molecular, imaging and clinical data, which facilitates identification of pretreatment profiles that are associated with disease-modifying antirheumatic drug response in psoriatic arthritis (PsA).
⇒ We use a two-step data analysis approach to both discover and validate predictive profiles.
⇒ Sensitive imaging techniques are used to evaluate treatment response at multiple time points, enabling comparison with conventional response measures.
⇒ Although the TOFA-PREDICT includes therapies with three different mechanisms of action (methotrexate, a tumour necrosis factor inhibitor and a Janus kinase inhibitor), this does not cover the full therapeutic armamentarium available for PsA.
⇒ The two-step approach with discovery and validation bisects the cohort, leading to reduced sample size per treatment group.

Trial registration number EudraCT: 2017-003900-28.

INTRODUCTION

Background

Psoriatic arthritis (PsA) is a chronic, autoinflammatory and autoimmune musculoskeletal disease that affects up to 30% of patients with psoriasis.[1] It is considered a heterogeneous disease, as patients have a variable disease course and clinical phenotype.[1–4] The hallmarks of PsA include cutaneous psoriasis, nail dystrophy, peripheral arthritis, axial spondyloarthritis, dactylitis and enthesitis.[1–3] PsA may also feature extramusculoskeletal manifestations and comorbidities that impact overall morbidity and mortality, including

anxiety, depression, uveitis, inflammatory bowel disease, metabolic syndrome and cardiovascular events.[5–11]

PsA can cause severe joint damage early in the disease course, contribute to functional disability and chronic pain and, as such, negatively impact quality of life.[2 4 12–14] Delayed treatment initiation is associated with progression of joint erosions, decreased long-term physical function and reduced risk of medication-free remission.[13–16] A delayed diagnosis of 6 months may already negatively impact physical function and joint erosions.[14] These data highlight the necessity of timely initiation of effective treatment with disease-modifying antirheumatic drugs (DMARDs).[17 18]

Challenges in treatment and assessing response to therapy

The care for patients with PsA faces several challenges.[19] The first challenge arises in unravelling the mechanisms that underlie pathogenesis. Although over the past 15 years many researchers have studied its complex aetiology, the exact molecular mechanisms underpinning PsA pathogenesis remain unknown.[3 20] It is important to improve our understanding of the genetic, environmental and immune-mediated factors that initiate and maintain the disease, as discoveries about dysregulated immunological pathways can facilitate the development of new therapies. For example, identification of the implications of the tumour necrosis factor (TNF) alpha and interleukin (IL)-23/IL-17 pathways have led to rapid development of effective therapeutic agents.[1 3] Moreover, stratification of patients with inflammatory arthritis by immunological phenotype for selection of therapy has shown promise. For example, favourable treatment response in patients with PsA who were stratified based on circulating T helper cell profiles has been reported.[21] In rheumatoid arthritis, a machine learning (ML) model based on divergent transcriptional signatures in peripheral blood mononuclear cells (PBMCs), monocytes and CD4+ T cells was reported to predict treatment response in adalimumab or etanercept (ETN)-treated patients.[22] These examples underline how unravelling disease pathogenesis may improve clinical practice.

The second challenge comprises a lack of methods to select the optimal treatment for each patient.[4 12 23] Evidence-based treatment strategies for PsA were developed by the European Alliance of Associations for Rheumatology (EULAR) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). However, treatment response rates are disappointing.[24 25] Up to 40% of patients respond insufficiently to a first DMARD, and strongly divergent drug responses are observed.[3 4 12] Although conventional synthetic (cs) DMARDs are frequently used as first-line therapy, there is limited evidence available on their effectiveness in PsA.[26–28] Moreover, the number of csDMARDs, biological (b)DMARDs and targeted synthetic (ts)DMARDs is rapidly increasing and head-to-head trials are scarce.[23 29–31] Hence, clinicians have no tools at their disposal to predict which DMARD will be effective for an individual patient.[23] This lack of precision medicine is a clinically relevant problem for a potentially aggressive disease that may impact quality of life, affect multiple organ systems, has an economic burden on the healthcare system and demands costly treatment that potentially causes adverse events.[12–19 21]

The third challenge comprises the wide array of novel imaging modalities and the growing number of analytical methods that have become available for the evaluation of therapy response in PsA. Conventional radiography lacks sensitivity, especially in patients with early disease in whom little radiographic abnormalities are observed.[32] Furthermore, the visual interpretation of medical images is time consuming, bound with interobserver variation and limited to semiquantitative outcomes that may be insensitive to detect small changes over time. On the contrary, computer-based medical image analysis can generate uniform, quantitative results in a (semi)automatic manner. Adding these techniques in trials and in clinical practice may add to unravelling mechanisms as well as improvement of treatment.

Rationale

Overall, there is an urgent clinical need to assess and understand the cellular and molecular pathways underlying DMARD treatment response in PsA. To this end, the TOFA-PREDICT trial was designed. In this investor-initiated, phase III, multicentre, four-arm randomised trial, a multiomics systems medicine approach is used to integrate pretreatment clinical, transcriptomic, metabolomic, proteomic, flow cytometric and imaging data to discover profiles of patients with PsA that predict response to tofacitinib (TOF), as compared with methotrexate (MTX) and ETN. By expanding our knowledge of the underlying mechanisms, course and treatment response, the TOFA-PREDICT study also aims to identify novel biomarkers for diagnosis and disease monitoring.[3 19]

In the TOFA-PREDICT trial, sensitive imaging techniques, including MRI and fluorine-18-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT), are applied to monitor disease activity. The current trial can deliver important data on the value of these more advanced imaging methods. With the use of ankle MRI scans early, possibly reversible and inflammatory features of PsA can be visualised at the heel, which is the most frequently affected site for enthesitis in PsA.[33 34] Moreover, ^{18}F-FDG PET/CT might aid in the measurement of local and systemic inflammation in PsA, including (peri) articular and vascular inflammation.

OBJECTIVES

Primary

- Identify pretreatment profiles with integrated clinical, transcriptomic, metabolomic, proteomic, flow cytometric and imaging data that predict response to treatment with TOF in DMARD-naïve and DMARD-non-responsive patients with PsA.

Secondary

- Compare clinical efficacy of treatment with TOF, MTX and ETN in DMARD-naïve and DMARD-non-responsive patients with active PsA.
- Compare structural response to treatment of active PsA with TOF, MTX and ETN using (semi)quantitative ankle MRI outcomes, radiographic outcomes and ^{18}F-FDG PET/CT outcomes.
- Determine (medication-specific) molecular mechanisms predicting and underlying clinical response to TOF, in comparison to MTX, and ETN in active PsA.

METHODS AND ANALYSIS

Study setting

TOFA-PREDICT is a multicentre (seven), investigator-initiated, phase III, open-label, four-arm randomised controlled study conducted in the Netherlands. A total of 160 patients with PsA who fulfil the Classification Criteria for Psoriatic Arthritis will be included in two groups, each with two treatment arms.[35] The first group consists of DMARD-naïve patients, who are randomised to MTX (arm 1) or TOF (arm 2). The second group consists of DMARD-non-responsive patients, who continue csDMARD background therapy and are randomised to addition of ETN (arm 3) or TOF (arm 4).

Eligibility criteria are displayed in table 1. The TOFA-PREDICT trial started on 4 April 2018 and the scheduled end date is 1 July 2025. By the end of 2022, inclusion of the first cohort of 80 patients is completed. The evaluation of the first cohort will be initiated early 2023.

Interventions

The first group of patients are DMARD naïve and have active PsA. Typically, these patients are at an early stage of PsA. Patients are randomised to receive either MTX monotherapy 25 mg once a week, subcutaneously (standard of care therapy, arm 1), or TOF monotherapy 5 mg two times per day, orally (investigational therapy, arm 2). Randomisation is performed per site in computer-generated random blocks. Patients will be assessed according to a predefined schedule of regular study visits (table 2). In case of treatment failure (see the 'Treatment failure' section), combination therapy will be initiated: patients randomised to MTX will also start TOF and vice versa. If drug intolerance warrants discontinuation of the drug, a switch will be made to the alternate drug as monotherapy (TOF to MTX and vice versa).

The second group of patients are non-responders to previous treatment with either MTX, leflunomide or sulfasalazine, or to previous treatment with combination therapy of a csDMARD and one previous bDMARD. A history of one bDMARD prior to inclusion is allowed, except for prior use of ETN. Prior use of a tsDMARD (Janus kinase inhibitor, abatacept) is also not allowed. Only patients who have had secondary treatment failure to a TNF inhibitor (TNFi), defined as initial good response, but diminished clinical efficacy over time, are eligible to participate in the study.[36] These DMARD non-responders continue background therapy with csDMARD and are randomised to receive the addition of either ETN 50 mg once a week, subcutaneously (arm 3), or TOF 5 mg two times per day, orally (arm 4). ETN was chosen as it was reimbursed and no preference for a specific TNFi is mentioned in current EULAR and GRAPPA international guidelines for the treatment of PsA.[24 25] In the event of treatment failure or drug intolerance (see the 'Treatment failure' section), a switch from ETN to TOF or vice versa will be made (figure 1).

Study visits

Study visits are performed at baseline and weeks 4, 16, 26, 39 and 52. Each study visit comprises multiple study assessments (a schematic overview is depicted in table 2). From week 16 onwards, the American College of Rheumatology (ACR)50 score is calculated every study visit to determine treatment failure.[37] The ACR50 score is described in the Outcomes section. Patients are evaluated additionally to the above-described visits according to regular clinical practice, including blood sampling for safety measurements according to regular practice. During all visits, adverse events and serious adverse events (SAE) are documented with respect to safety.

Treatment failure

Treatment failure is defined as failing to achieve an ACR50 response on two consecutive visits from week 16 onwards. If a patient does not attain the ACR50 response at a regular study visit, an additional study visit is scheduled 4 weeks later. At this 'treatment failure' visit the ACR50 response is reassessed. In the event that the ACR50 response is again not attained, 'treatment failure' is confirmed and a crossover to the alternate treatment protocol within that study group takes place (figure 1). A minimum washout of 1 week will be applied to patients switching from TOF to ETN (or vice versa). If the ACR50 response is attained at the 'treatment failure' visit, regular 12-week visit intervals will continue and the patient will not switch therapy. In addition, drug intolerability that warrants discontinuation (eg, side effects, laboratory abnormalities) is defined as treatment failure at any time point. In the case of MTX, dosage lowering is the first step in case of drug intolerability. For ETN and TOF, dosage changes are not possible and drug intolerability indicates treatment failure. Crossover will not take place in the last 3 months of follow-up.

MTX dosage adjustments

MTX is initiated in the DMARD-naïve arm at a dosage of 15 mg/week subcutaneously. The dosage is increased to 25 mg/week after 4 weeks, unless the ACR50 response is attained or side effects prevent safe dosage escalation. By increasing the dosage to 25 mg/week at week 4, the primary end point of the study can be compared between MTX and TOF at week 16 (ie, 12 weeks of administering the maximal dosage of MTX). MTX dosage may be reduced during follow-up if ACR50 has been attained

Table 1 Eligibility criteria, TOFA-PREDICT

Inclusion criteria	
General	
1	Patients aged 18–75 years.
2	Fulfilment of CASPAR criteria for psoriatic arthritis (PsA).
3	PsA disease duration ≥8 weeks.
4	Active arthritis based on ≥2 swollen joints and ≥2 tender joints.
Concomitant therapies	
5	In case of oral corticosteroid use, a stable dose of ≤10 mg/day of prednisone (or equivalent) for ≥4 weeks prior to baseline visit is allowed.
6	In case of NSAID use, a stable dose 1 week prior to baseline visit is allowed.
7	In case of current topical treatment of psoriasis, the following regimens are allowed: ► Non-medicated emollients. ► Topical corticosteroids ≤1% for only palms, soles, face and intertriginous areas. ► Tar or salicylic acid preparations and shampoos for only the scalp.
Specific for DMARD-non-responsive patients (arms 3 and 4)	
8	Current use of csDMARD (MTX, LEF, SSZ): ► On the highest tolerable dosage (max dose 25 mg/week). ► A stable dose ≥4 weeks prior to baseline. ► Without previous serious toxicity. ► In case of MTX: concomitant folate supplementation ≥5 mg/week.
9	History of 1 bDMARD prior to inclusion is allowed, except: ► Prior use of etanercept. ► Primary failure of other TNFi than etanercept (adalimumab, golimumab, infliximab, certolizumab).
Exclusion criteria	
General	
10	Pustular psoriasis only.
11	Diagnosis of fibromyalgia or history of any rheumatic autoimmune or inflammatory disease other than PsA.
12	Any condition possibly affecting oral drug absorption, such as gastrectomy, diabetic gastroenteropathy or bariatric surgery (eg, gastric bypass).
13	A skin condition at the time of baseline that could interfere with evaluation of psoriasis severity.
14	Previous participation in any study with tofacitinib as IP.
15	Participation in other studies involving investigational drug(s) ≤4 weeks prior to baseline visit.
Specific for DMARD-naïve patients (arms 1 and 2)	
16	History of csDMARD, bDMARD or tsDMARD use.
Specific for DMARD-non-responsive patients (arms 3 and 4)	
17	History of ≥2 bDMARDs or ≥1 tsDMARD.
Therapies	
18	Prior treatment with non-B cell-specific lymphocyte depleting therapies, alkylating agents or total lymphoid irradiation. Rituximab or other selective B lymphocyte-depleting agents are allowed, if discontinued ≥1 year prior to first dose of the IP and normal CD19/20+ counts by flow cytometry analysis.
19	Specific concomitant therapies, being: ► Injected corticosteroids ≤4 weeks prior to baseline visit. ► UVB phototherapy ≤2 weeks prior to baseline visit. ► Psoralens and UVA (PUVA) phototherapy ≤4 weeks prior to baseline visit. ► Topical treatments that could affect psoriasis severity (corticosteroids, tars, keratolytics, anthralin, vitamin D analogues, retinoids) ≤2 weeks prior to baseline visit.
Safety	
20	Pregnant females, females planning pregnancy, breastfeeding females and females of childbearing potential not using highly effective contraception. Women of childbearing age must test negative for pregnancy prior to enrolment.

Continued

Table 1 Continued

Exclusion criteria	
21	Blood dyscrasias within 3 months prior to baseline visit, including: ► Haemoglobin <100 g/L. ► White cell count <3.0×10^9/L (<3000/mm^3). ► Absolute neutrophil count ≤1.5x10^9/L (<1500/mm^3). ► Absolute lymphocyte count <1.0×10^9/L (<1000/mm^3). ► Platelet count <100×10^9/L (<100 000/mm^3).
22	Estimated creatinine clearance <40 mL/min based on Cockcroft formula.
23	Total bilirubin, AST or ALT more than two times the upper limit of normal at screening visit.
24	History of an infected joint prosthesis at any time, with the prosthesis still in situ.
25	Oral antimicrobial therapy ≤2 weeks prior to baseline visit.
26	Vaccination with live or attenuated vaccines: ► ≤6 weeks prior to baseline visit. ► Planned during the study period. ► ≤6 weeks following discontinuation of the IP.
27	History of alcohol or drug abuse (unless in full remission for ≥6 months prior to baseline visit).
28	Significant trauma or surgical procedure ≤1 month prior to baseline visit, or any planned elective surgery during the study period.
29	Active, latent or inadequately treated infection with *Mycobacterium tuberculosis* as defined by: ► Positive QuantiFERON-TB Gold In-Tube test within 3 months prior to the screening visit. ► Suspected radiographic features on chest radiograph within 3 months prior to the screening visit. ► Medical history of inadequately or untreated latent or active *M. tuberculosis* infection.
30	Positive serological screening for infection with HIV, hepatitis B virus, hepatitis C virus or history of any other chronic infection.
31	Increased risk for gastrointestinal perforation, such as diverticulitis.
32	History of any immunodeficiency or a first-degree relative with a hereditary immunodeficiency.
33	History of any lymphoproliferative disorder (such as Epstein-Barr virus-related lymphoproliferative diseases), history of lymphoma, leukaemia or signs and symptoms suggestive of current lymphatic disease.
34	History of a disseminated herpes zoster or simplex infection, or recurrent (≥1 episode) herpes zoster infections.
35	History of active infection requiring hospitalisation, parenteral antimicrobial therapy or as otherwise judged clinically significant by the investigator, ≤6 months prior to baseline visit.
36	Current history of lymphoma and malignancy, except for: ► Adequately treated or excised non-metastatic basal cell cancer of the skin, squamous cell cancer of the skin and cervical carcinoma in situ. ► Adequately treated solid malignant tumours without recurrence after a minimal follow-up period of 10 years.
37	Current or recent history of a severe, progressive or uncontrolled renal, hepatic, haematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular or neurological disease.
38	Other severe acute or chronic, medical or psychiatric conditions, or laboratory abnormalities, that may: ► Increase the risk associated with study participation or IP administration. ► Interfere with interpretation of study results.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; bDMARD, biological DMARD (eg, inhibitors of tumour necrosis factor and interleukin-17A); CASPAR, Classification Criteria for Psoriatic Arthritis; csDMARD, conventional synthetic DMARD (eg, methotrexate, leflunomide or sulfasalazine); DMARD, disease-modifying antirheumatic drug; IP, investigational product; LEF, leflunomide; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; SSZ, sulfasalazine; TNFi, tumour necrosis factor inhibitor; tsDMARD, targeted synthetic DMARD; UVA, ultraviolet A; UVB, ultraviolet B.

and/or if side effects occur, in accordance with standard clinical care.

Escape medication

In accordance with standard clinical care, the following escape therapies are allowed: non-steroidal anti-inflammatory drugs, intra-articular corticosteroid injections and, from week 24 onwards, topical corticosteroids.

End of study

After 52 weeks of follow-up, all patients will resume regular clinical care while continuing the DMARD therapy that was initiated during the study. Treatment in regular care will also be resumed by patients who discontinue trial medication due to (serious) adverse events, treatment failure after crossover or other reasons. From

Table 2 Schematic overview of study assessments

Category	Assessment	Screening	Baseline	FU	Primary end point	FU	FU	End of study	Treatment failure*
	Week number	n.a.	0	4	16	26	39	52	tbd
Eligibility	Signed informed consent	√							
	Medical history	√							
	Inclusion and exclusion criteria	√	√						
	Randomisation		√						
Anamnestic	Online questionnaires†		√	√	√	√	√	√§	√
	Patients' well-being	√	√	√	√	√	√	√§	√
	Adverse event evaluation		√	√	√	√	√	√§	√
	Medication annotation	√	√	√	√	√	√	√§	√
Physical examination	Length		√						
	Weight		√	√	√	√	√	√	√
	Vital signs‡		√	√	√	√	√	√	√
	Basic physical examination		√	√	√	√	√	√	√
	TJC (76) and SJC (78)		√	√	√	√	√	√§	√
	Dactylitis evaluation		√	√	√	√	√	√§	√
	Leeds Enthesitis Index and enthesis plantar fascia		√	√	√	√	√	√§	√
	PASI and BSA		√	√	√	√	√	√§	√
	VAS physician		√	√	√	√	√	√§	√
Blood sample	Clinical chemistry and haematology¶	√		√	√	√	√	√§	
	Systems medicine approach**		√	√	√			√	√
Imaging	X-rays (hands, feet)		√					√§	
	MRI (ankles)		√		√			√	
	^{18}F-FDG PET/CT (whole body)		√					√	
Evaluation	Response				√	√	√	√§	√

*A 'treatment failure visit' is planned when the ACR50 response is not attained at a regular study visit; starting from week 16. Treatment failure is defined as again not attaining the ACR50 at this extra study visit 4 weeks later.
†Questionnaires: Assessment of SpondyloArthritis International Society (ASAS) Health Index, Dermatology Life Quality Index (DLQI), EuroQol-5 Dimension (EQ-5D) Scale, Health Assessment Questionnaire (HAQ), Self-Administered Psoriasis Area and Severity Index (SAPASI) and the Work Productivity and Activity Impairment (WPAI) Questionnaire, supplemented by the visual analogue scale (VAS) for general well-being and pain.
‡Vital signs: blood pressure, pulse and temperature (auricular measurement).
§Selection of data obtained after resuming treatment in regular care for patients who discontinue trial medication due to (serious) adverse events, treatment failure after crossover or other reasons.
¶At screening visit: hepatitis B surface antigen (HbsAg), hepatitis B core IgG, HIV-1 and 2 antibodies, p24 antigen, interferon-γ release assay (IGRA), rheumatoid factor (RF), anti-citrullinated peptide/protein antibodies (ACPAs), haemoglobin (Hb), haematocrit (Ht), thrombocytes, erythrocytes, leucocytes and differentiation, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatinine, estimated glomerular filtration rate (eGFR), sodium, potassium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, glycosylated haemoglobin (HbA1c), triglycerides and cholesterol (total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL)). At follow-up visits: Hb, Ht, thrombocytes, erythrocytes, leucocytes, ESR, CRP, ALT, eGFR, triglycerides and cholesterol.
**Systems medicine approach to collect '-omics' data: proteomics, transcriptomics and metabolomics. At baseline, week 4, week 16 and week 52, a total of 85 mL blood is drawn for isolation of serum, plasma, peripheral blood mononuclear cells (PBMCs), B cells, myeloid dendritic cells (mDCs), monocytes and peripheral blood leucocytes (PBLs). In case of treatment failure only 35 mL blood is drawn for isolation of serum, plasma and PBMCs.
††
ACR, American College of Rheumatology; BSA, body surface area; ^{18}F-FDG PET/CT, fluorine-18-fluorodeoxyglucose positron emission tomography/CT; FU, follow-up; n.a., not available; PASI, Psoriasis Area and Severity Index; SJC, swollen joint count; tbd, to be determined; TJC, tender joint count; X-ray, conventional radiographic photograph.

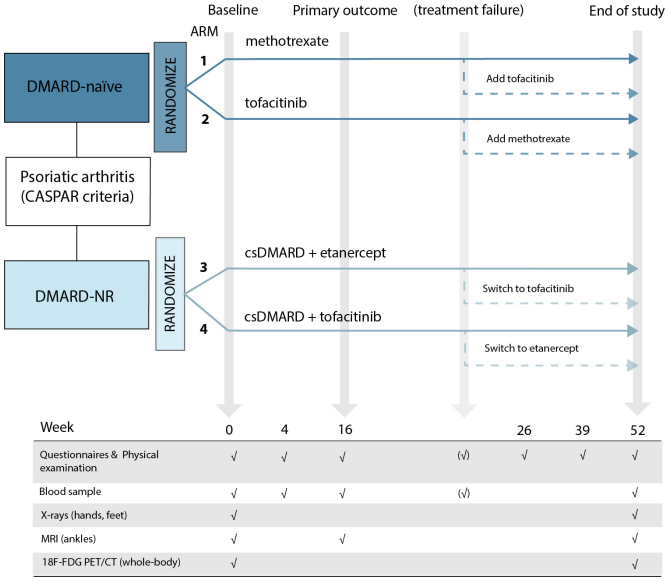

Figure 1 Study design. Treatment failure is defined as not attaining the ACR50 response on two consecutive study visits (interval of 4 weeks), starting from week 16. ACR, American College of Rheumatology; CASPAR, Classification Criteria for Psoriatic Arthritis; csDMARD, conventional synthetic disease-modifying antirheumatic drug; ^{18}F-FDG PET/CT, fluorine-18-fluorodeoxyglucose positron emission tomography/CT; NR, non-responder to conventional synthetic and a maximum of one biological DMARD therapy.

these patients, we will only collect a selection of data after 52 weeks of follow-up (table 2: footnote §).

Data collection and samples

All collected clinical data are entered in an online database (research online; Julius Center University Medical Center (UMC) Utrecht) designed for the TOFA-PREDICT trial. Blood samples for the multiomics analyses are collected at several time points throughout the study (figure 1). In addition, blood samples are taken to monitor drug safety after the start of MTX, TOF or ETN. Blood samples for the multiomics analyses are collected at seven different study sites. After protocolised transport, all blood samples are processed in a standardised way in the UMC Utrecht. The samples are pseudoanonymised and after magnetic-activated cell sorting, PBMC subsets are stored. Additionally, serum, plasma and PBMC subset lysates are stored. All blood samples for multiomics analyses are registered with Quaero Systems. The multiomics analyses of the stored samples are performed in batches at a later stage, taking confounders such as treatment arm, visit number and demographics into account. All data are integrated at the Data Research Environment (anDREa). The omics data will be made available in public databases after primary analyses and publication.

Patient and public involvement

Patients were not involved in the development of the research question, the design and conduct of the study, choice of outcome measures nor recruitment.

Outcomes

Systems medicine approach

The primary objective is to discover and validate pretreatment clinical, transcriptomic, metabolomic, proteomic, flow cytometric and imaging profiles that predict treatment response. Response and non-response are defined as attaining or not attaining minimal disease activity (MDA), respectively, after 16 weeks of treatment. To define these profiles, a multiomics systems medicine approach will be used for which transcriptomic, metabolomic, proteomic and flow cytometric data are collected. Transcriptomic and flow cytometric analysis will be performed on PBMC (subset)s. Proteomic and metabolomic analyses will be performed on serum and/or plasma samples. These molecular and cellular data will be added to the clinical, structural and imaging data (ankle MRIs, whole-body ^{18}F-FDG PET/CT and radiographs of the hands and feet). Systems medicine data analyses will be used to combine the different omics layers in our attempt to identify profiles that predict treatment response.

Clinical efficacy measures

We use MDA at week 16 as the primary outcome for the identification of molecular and cellular profiles that predict treatment response. MDA is a validated, PsA-specific composite measure that includes evaluation of arthritis (tender and swollen joint count), skin disease (Psoriasis Area and Severity Index and body surface area), enthesitis and patient-reported outcomes (Health Assessment Questionnaire (HAQ), visual analogue scale (VAS) for pain and VAS for patient global assessment).[38 39] The clinical relevance of composite measures that include multiple disease domains has become increasingly evident over recent years.[38–40] To define treatment failure, we use the ACR50 response because treatment effect during follow-up is most commonly detected as a change from baseline. ACR50 is a composite measure defined as 50% improvement in the number of both swollen and tender joints, next to 50% improvement in at least three of the following outcomes: HAQ, acute phase reactant (we use C-reactive protein), VAS for patient global assessment, VAS for physician global assessment and VAS for pain.[37 41 42] We calculate the ACR50 every 12 weeks starting from week 16. Moreover, we assess dactylitis, blood pressure, body mass index, laboratory parameters and additional patient-reported outcomes, and calculate additional PsA-specific composite indices.[43]

Patient-reported measures

At baseline, weeks 4, 16, 26, 39, 52 and at treatment failure visits, patients fill out online questionnaires to monitor disease activity and their mental and physical health. TOFA-PREDICT employs the following questionnaires: Assessment of SpondyloArthritis International Society Health Index, Dermatology Life Quality Index, EuroQol-5 Dimension Scale, HAQ, Self-Administered Psoriasis Area and Severity Index, the Work Productivity and

Activity Impairment Questionnaire and two VAS scores to assess pain and the patients' global assessment.[44–49]

Imaging measures

Three imaging techniques are applied in the TOFA-PREDICT study: MRI scans of both ankles, whole-body ^{18}F-FDG PET/CT and conventional radiography of the hands and feet. At baseline, week 16 and week 52, MRI scans of both ankles are obtained. MRI scans are performed using MR equipment with a field strength of 1.5 or 3 T. The ankles are scanned separately using an extremity coil. The MRI protocol was developed in accordance with the European Society of Musculoskeletal Radiology recommendations and contains the following sequences: 3D proton density with fat suppression (FS), transversal T1 turbo spin echo and 3D T1 FS before and after intravenous gadolinium injection.[50] The estimated total time in the MRI room is <60 min per patient per visit. Ankle MRIs are visually evaluated using Psoriatic Arthritis Magnetic Resonance Imaging Scoring System (PsAMRIS), adapted for the heel, and (Heel Enthesitis Magnetic Resonance Imaging Scoring System (HEMRIS) measures.[33 51] Using deep learning, quantitative outcome measures for ankle MRIs will be developed aiming to quantify (peri)articular inflammatory joint changes such as synovitis, bone marrow oedema and enthesitis.

At baseline and week 52, whole-body ^{18}F-FDG PET/CT scans are obtained. ^{18}F-FDG is administered intravenously after an overnight fast. Dosing of ^{18}F-FDG depends on local guidelines. After administration of ^{18}F-FDG, the ^{18}F-FDG PET/CT is performed 1 hour later. A non-contrast-enhanced low-dose CT is performed for attenuation correction. In this multicentre trial, all PET/CT reconstructions are compliant to European Association of Nuclear Medicine Research Ltd guidelines in order to achieve comparable quantitative outcome parameters, such as standardised uptake values.[52] The main ^{18}F-FDG PET/CT outcome measures are vascular and (peri)articular inflammation.

At baseline and at week 52, radiographs of hands and feet are acquired. Radiographs of hands and feet are evaluated using the PsA-modified Sharp-van der Heijde score.[53] MRI, ^{18}F-FDG PET/CT and radiography observers are blinded to diagnosis and treatment.

Sample size calculation

The primary objective of TOFA-PREDICT is to predict the treatment response (attaining or not attaining MDA after 16 weeks of treatment in active PsA) using the multiomics analysis of pretreatment omics data. To evaluate the sample size needed to detect differentially expressed genes/proteins (DEGPs) between responders and non-responders we simulated several scenarios. These scenarios used a range of number of prognostic genes (50–500), dispersion (0.1–0.5) and false discovery rates (FDR; 0.01–0.1) within each scenario assuming a minimum fold change in DEGPs of 2, 80% power and testing of a total of 20 000 genes with a mean expression (read count) of 50. Separate analyses were performed for an equal distribution between responders and non-responders (50:50) and for unequal distributions of responders and non-responders (40:60 and 25:75). Results in the scenario assuming 400 differentially expressed genes, an FDR of 0.05 and an unequal distribution between responders and non-responders (40:60) assuming dispersion values as found in previous RNA-seq data from our group (eg, CD14+ monocytes, dispersion value 0.11) resulted in a sample size of 20 patients per arm. Therefore, we assumed a sample size of 80 (20 patients per arm) to be sufficient to detect relevant expression signatures. Sample size was calculated using the R package 'RnaSeqSampleSize' (V.3.6.1).[54] For other omics platforms, required sample sizes are considered smaller based on the smaller number of markers (eg, proteins up to 180 and metabolites up to 800). To enable external validation, a similar cohort will follow the first 80 patients up to a total of 160 included patients.

Data analyses

Systems medicine approach

Different layers of baseline omics data will be analysed separately and will be integrated with clinical parameters (eg, gender, disease duration, etc), patient-reported parameters and imaging data for the discovery and validation of molecular and cellular signatures that serve as biomarkers to predict treatment response after 16 weeks of treatment (primary end point). Furthermore, molecular signatures will be computed using omics data collected at weeks 4 and 52 (or treatment failure) in addition to baseline data. We will explore the molecular signatures using bioinformatic approaches. The observations made during the exploration of the data will guide the choice of tools and algorithms for the next step of the data analysis.[55] For each analysis step, we will perform permutation analysis and k-fold cross-validation to test the reliability of the molecular signature. Moreover, we will integrate multiomics data to discover molecular signatures that are supported by different layers of data, strengthening the reliability of the discovered signature. For prediction at baseline, the expression (ie, fold change) of the separate omics layers will be analysed. Thereafter, using resulting relevant expression signatures in addition to established clinical and imaging predictors as features, we will build integrated and internally validated ML models to predict response to TOF and separately response to MTX and ETN. A final statistical analysis plan (SAP) will be defined prior to database lock using the optimal techniques for analysing expression profiles and optimal ML models to use. Genes or gene modules from these signatures and models will bring forth new hypotheses that can be verified experimentally, contributing towards a better understanding of the disease mechanisms and a predictive model for disease outcome and therapy response.

Two-step analysis

After inclusion of the first 80 patients (~20 patients per group), the first step of the predictive multiomics analysis will be performed. Of all the available multiomics data, predictive biomarkers are identified as either relevant (statistically significant), irrelevant (statistically insignificant) or promising (based on clinical and scientific reasons without formal statistical significance). For each omics platform, an optimal predictive assay for treatment response will be developed. Also, all relevant biomarkers will be integrated in multiomics approaches and added to clinical data and structural imaging data to develop an exploratory prediction model for treatment response. To externally validate the identified biomarkers, we implement a second step in the analysis. Both the relevant and promising biomarkers will be analysed in the subsequent cohort of 80 patients to replicate the results from the first phase. The proposed omics assays from the first cohort will be validated in the second cohort. Finally, the combined relevant and promising biomarkers of all 160 patients will be integrated in multiomics approaches and added to structural imaging data and clinical data to develop a final and clinically applicable prediction model using pretreatment markers. In this phase, the added predictive value of omics markers over known, easily available (clinical) baseline predictors will also be assessed.

Clinical efficacy and structural response

Efficacy of treatment and imaging outcomes will be compared between different treatment arms using logistic or linear regression analyses taking into account established prognostic indicators (such as structural damage, elevated acute phase reactants and polyarthritis, to be finalised in the SAP) and centre (as the stratification factor used in randomisation). The significance level (α) will be set at 0.05, with p values less than or equal to α considered statistically significant.

Missing data and SAEs

Cases that are lost to follow-up and other missing data will be presented descriptively. If the percentage of missing data exceeds 5%, multiple imputation will be performed, based on data type and quantity of the missing data. For binary secondary drug efficacy outcomes, missing data will be defined as non-response to prevent overestimation of the effect. SAEs and suspected unexpected serious adverse reactions will be reported descriptively.

ETHICS AND DISSEMINATION

Ethics approval and informed consent

The study was approved by the Medical Research Ethics Committee in Utrecht, Netherlands (MREC reference number: NL63439.041.17), and is carried out in accordance with the Declaration of Helsinki. The trial is registered in the European Clinical Trials (EudraCT) Database (reference number: 2017-003900-28). All participants provided written informed consent. The study progress is monitored by a science-driven contract research organisation (Julius Clinical).

Dissemination plan

The results of the primary and secondary objectives of the study will be published in international peer-reviewed journals and on national and international scientific conferences.

Author affiliations
[1]Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands
[2]Radiology, UMC Utrecht, Utrecht, The Netherlands
[3]Center for Translational Immunology, University Medical Center Utrecht, Utrecht, The Netherlands
[4]Image Sciences Institute, University Medical Center Utrecht, Utrecht, The Netherlands
[5]Orthopedics, University Medical Center Utrecht, Utrecht, The Netherlands

Twitter Juliëtte N Pouw @UMCURRCI

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Contributors All authors substantially contributed to discussion, reviewing, revising and improvement of the protocol and writing of the manuscript before submission. FTP, NJK, JNP and NLAV are the lead investigators. FL and MH are the principal instigators. JT and JS provided clinical input and supervision of research clinicians. EFAL contributed to study design. PW is responsible for methodology and statistics in the design and analysis of the study. MH, PW, FL and SAYH contributed to the analysis plan and processing of blood samples. WF, MPJ, SA, FL and PAdJ are responsible for imaging in design and completion of the study. In each participating site, a lead investigator (rheumatologist) is responsible for identification, recruitment, data collection and completion of CRFs, follow-up of study patients, adherence to study protocol and investigators' brochure and participation in feedback sessions during the conduct of this study. Lead investigators and other contributing colleagues in the participating sites are listed in the TOFA-PREDICT author group.

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ORCID iDs
Frank T Perton http://orcid.org/0000-0001-7331-0104
Juliëtte N Pouw http://orcid.org/0000-0002-1818-7833
Nanette L A Vincken http://orcid.org/0000-0003-2892-4814

Mylène P Jansen http://orcid.org/0000-0003-1929-6350
Wouter Foppen http://orcid.org/0000-0003-4970-8555
Julia Spierings http://orcid.org/0000-0002-2546-312X

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