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SATURN: Effect of secukinumab in the treatment

Submission date
18/07/2016

Recruitment status
No longer recruiting

Registration date
21/07/2016

Overall study status
Completed

Last Edited
23/06/2020

Condition category
Musculoskeletal Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Psoriatic arthritis (PsA) is a type of arthris that usually develops in people with the skin condition psoriasis (a skin condition that causes red, flaky, crusty patches of skin covered with silvery scales). PsA causes painful inflammation (swelling) and stiffness in the joints. In PsA, like in psoriasis alone, it is thought to be caused by the immune system mistakenly attacking healthy tissue (autoimmune disease). This study is being carried out to investigate the effects of a drug called secukinumab on patients with psoriatic arthritis. Secukinumab is medication which works by reducing the effects of chemical substances in the body that lead to inflammation (immunosuppressant). This will be done by investigating the effects on components of the blood, including white blood cells (which fight infection), vitamin D and cytokines (small proteins that help cells communicate with each other) in people with PsA and on the blood of healthy participants.

Who can participate?
Adults with PsA who have not previously had biologic therapy and healthy adults who are employed at University of Liverpool or Aintree University hospitals.

What does the study involve?
Eligible patients are registered into the study and receive four injections just below the skin (subcutaneous injections) of 150 - 300 mg subcutaneous injections at weekly intervals, followed by regular injections of 150mg once a month for a total of 12 months, as well as standard treatment with normal disease-modifying antirheumatic drugs (DMARDs, a group of drugs used to treat arthritis by reducing inflammation and reducing damage to the joints). At the start of the study, and then after 3, 6, 9 and 12 months, participants have a sample of blood taken so that white blood cell, vitamin D and cytokine concentrations can be measured. The healthy participants provide a sample of blood at the same time points which is then tested for neutrophil (a type of white blood cell which help fight infection by ingesting microorganisms and releasing enzymes that kill the microorganisms) levels, which are then compared to the results of the participants with PsA.

What are the possible benefits and risks of participating?
There are no direct benefits involved with participating in this study. There is a small risk of pain, bruising or infection when blood samples are taken.

Where is the study run from?
Aintree University Hospital NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
June 2014 to February 2019

Who is funding the study?
Novartis Pharma AG (UK)

Who is the main contact?
Prof. Robert Moots
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

ClinicalTrials.gov (NCT)
NCT02854163

Clinical Trials Information System (CTIS)
2015-004502-42

Protocol serial number
30782

Study information

Scientific Title
SATURN: An exploration of the dynamic interaction between IL-17, IL-17 inhibition with (secukinumab) and neutrophils in psoriatic arthritis in vitro and ex vivo with exploratory study on the potential role of Vitamin D

Acronym
SATURN

Study objectives
The aim of this study is to investigate, in detail, the clinical and molecular effects of IL-17 and inhibition of IL-17 with secukinumab, on neutrophil function in vitro and ex vivo. In addition, the secondary and exploratory aims are to explore the potential relationship between vitamin D on neutrophil function and response to IL-17 inhibition in psoriatic arthritis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North West - Liverpool Central Research Ethics Committee, 10/02/2016, ref: 16/NW/0006

Primary study design
Interventional

Study design
Interventional; Design type: Treatment, Drug, Immunotherapy

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Specialty: Musculoskeletal disorders, Primary sub-specialty: Inflammatory arthritis; UKCRC code/ Disease: Musculoskeletal/ Other disorders of the musculoskeletal system and connective tissue

Interventions
Interventions as of 23/05/2017:
Eligible patients with PsA are registered into the study.

Participants are treated with Secukinumab and receive four 150 - 300 mg subcutaneous injections at weekly intervals, followed by regular injections 150mg once a month thereafter for a total of 12 months, in addition to standard disease-modifying anti-rheumatic drugs (DMARD) therapy

Participants are followed up a 3, 6, 9 and 12 months post treatment.

The healthy controls will be recruited from staff at the University of Liverpool or Aintree University hospitals and who are not taking nor have taken over the preceding 6 months, any immunosuppressive agent including systemic corticosteroids and whose health is otherwise good. There will be an equal balance of males to females. The healthy controls will provide one sample of blood for neutrophil studies (in vitro work). The effects of adding exogenous IL-17 and of inhibiting this cytokine by secukinumab, on highly-purified neutrophils isolated from the blood of 10 healthy controls, will be determined. Neutrophil survival will be recorded together with full details on priming of respiratory burst, expression of integrins and other opsono-receptors, apoptosis, phagocytosis and chemotaxis. Experiments will be repeated after neutrophil preparations have been “spiked” with contaminating PBMC’s. If these experiments

indicate that the effects of IL-17 on neutrophils are indirect, we will determine the mechanism of PBMC activation. For example, this will include measurement of IL-17 derived neutrophil activating cytokines (by ELISA or multiplex) and/or using blocking monoclonal antibodies.

Original interventions:
Patients with PsA are allocated to intervention and control arms in a 4:1 ratio by means of computer generated random permuted blocks of size 5. No stratification factors are included.

Control arm: Participants receive standard disease-modifying anti-rheumatic drugs (DMARD) therapy. This includes Methotrexate (5mg-25mg orally or subcutaniously) once a week, Sulphasalazine (500mg-1g orally) twice a day and Leflunomide (10mg-20mg orally) once a day for 12 months.

Intervention arm: Participants are treated with Secukinumab and receive four 150 - 300 mg subcutaneous injections at weekly intervals, followed by regular injections 150mg once a month thereafter for a total of 12 months, in addition to standard DMARD therapy (as above).

Participants in both groups are followed up a 3, 6, 9 and 12 months post treatment.

The healthy controls will be recruited from staff at the University of Liverpool or Aintree University hospitals and who are not taking nor have taken over the preceding 6 months, any immunosuppressive agent including systemic corticosteroids and whose health is otherwise good. There will be an equal balance of males to females. The healthy controls will provide one sample of blood for neutrophil studies (in vitro work).
The effects of adding exogenous IL-17 and of inhibiting this cytokine by secukinumab, on highly-purified neutrophils isolated from the blood of 10 healthy controls, will be determined. Neutrophil survival will be recorded together with full details on priming of respiratory burst, expression of integrins and other opsono-receptors, apoptosis, phagocytosis and chemotaxis. Experiments will be repeated after neutrophil preparations have been “spiked” with contaminating PBMC’s. If these experiments indicate that the effects of IL-17 on neutrophils are indirect, we will determine the mechanism of PBMC activation. For example, this will include measurement of IL-17 derived neutrophil activating cytokines (by ELISA or multiplex) and/or using blocking monoclonal antibodies.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Secukinumab

Primary outcome(s)
1. Neutrophil phenotype is measured by quantifying receptor expression (n=7) using flow cytometry assays at baseline, 3, 6 and 12 months post treatment
2. Neutrophil lifespan is measured by quantifying apoptosis using flow cytometry assays at baseline, 3, 6 and 12 months post treatment
3. Function and production of IL-17 in response to secukinumab is measured using ELISA assays at baseline, 3, 6 and 12 months post treatment on healthy controls

Key secondary outcome(s)
1. Vitamin D status is measured using routine blood test measuring the amount of Vitamin D at baseline, 3, 6 and 12 months post treatment
2. Vitamin D receptor is measured using flow cytometry assays at baseline, 3, 6 and 12 months post treatment
3. Clinical response is measured using ACR20, PASI75, PASI90 and NAPSI measurements at baseline, 3, 6, 9 and 12 months post treatment
4. Quality of Life is measured using EQ5D and HAQ scores collected at baseline, 3, 6, 9 and 12 months post treatment
5. Toxicity is measured by the number and percent of patients with adverse event, serious adverse events, infections and serious infections, malignancies, acute injection site reactions and immunogenicity at baseline, 3, 6, 9 and 12 months post treatment

Completion date
28/02/2019

Eligibility

Key inclusion criteria
Inclusion criteria for healthy controls:
1. Not taking or have taken over the preceding 6 months any immunosuppressive agents including corticosteroid
2. Healthy
3. Able to given consent
4. Aged over 18 years

Inclusion criteria for Patients with PsA:
1. Active psoriatic arthritis (fulfilling CASPAR criteria) affecting ≥2 peripheral joints (swollen and tender) that have not responded to at least one standard DMARDs
2. All meet CASPAR criteria for diagnosis of PsA
3. Be rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) negative at screening
4. Have had no prior exposure to biologic therapy
5. Not have received parenteral glucocorticosteroids in the 6 weeks prior to the baseline assessment
6. If taking oral glucocorticoids remain on a stable dose of <10mg throughout the study with no change in dose in the 6 weeks prior to baseline assessment,
7. If taking methotrexate or other DMARDs remain on a stable dose throughout the study and not have changed dose or therapy for 6 weeks prior to the baseline assessment
8. Able to given consent
9. Aged over 18 years

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit

18 Years

Sex
All

Total final enrolment
19

Key exclusion criteria
Exclusion criteria for healthy controls:
Taking or have taken over the preceding 6 months any immunosuppressive agents including corticosteroid.

Exclusion criteria as of 23/05/2017:
Exclusion criteria for Patients with PsA:
1. Active or chronic infection including mycobacterium tuberculosis, HIV, hepatitis B or C , Hep B or C
2. Absence of active psoriatic arthritis
3. Patients who are starting anti-TNF therapy for treating PsA
4. Pregnancy and planning pregnancy
4.1. WOCBP who are unwilling or unable to use acceptable method to avoid pregnancy for study duration plus timeframe as specified in section 5.2.5.
4.2. Women who are pregnant or breastfeeding
4.3. Sexually active fertile men not using effective birth control if their partners are WOCBP.
5. Malignancy
6. Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process obtained within 3 months prior to Screening and evaluated by a qualified physician
7. Patients with hyponaetraemia and nephrotic syndrome
8. Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor
9. Use of any investigational drug and/or devices within 4 weeks before randomization registration or a period of 5 half-lives of the investigational drug, whichever is longer
10. Significant comorbidity that, in the opinion of the investigator, would impact on ability to participate
11. Any change in the dose of oral glucocorticosteroids or DMARDS in the prior 6 weeks prior to the Baseline visit or use of i.v. intramuscular or intra-articular glucocorticosteroid during the last 6 weeks prior to the enrollment visit
12. Patients who have previously been treated with TNFα inhibitors (investigational or approved)
13. History of hypersensitivity to the study drug or its excipients or to drugs of similar classes
14. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 investigational agents (e.g. CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)
15. Active ongoing inflammatory diseases other than PsA that might confound the evaluation of the benefit of secukinumab therapy
16. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine,cardiac, infectious or gastrointestinal conditions which in the opinion of the Investigator immunocompromise the patient and/or place the patient at unacceptable risk for participation in an immunomodulatory therapy
17. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥ 160/95 mmHg), congestive heart failure (New York Heart Association status of class III or IV), uncontrolled diabetes
18. History of clinically significant liver disease or liver injury as indicated by abnormal liver

function tests (LFT) such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria:
18.1. Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization registration, to rule out laboratory error.
18.2. If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed 1.6 mg/dL (27 µmol/L)
19. History of renal trauma, glomerulonephritis, or patients with 1 kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6 µmol/L)
20. Screening total white blood cell (WBC) count < 3 000/µL, or platelets < 100 000/µL or neutrophils < 1 500/µL or hemoglobin < 8.5 g/dL (85 g/L)
21. Active systemic infections during the last 2 weeks (exception: common cold) prior to registration
22. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis according to local practice/guidelines) or a positive QuantiFERON TB-Gold test or TB-Spot Test (as indicated in Section 4.1 and Table 6-1). Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated
23. Known infection with human immunodeficiency virus, hepatitis B or hepatitis C at Screening or registration
24. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed)
25. Use of Vitamin D containing supplements
26. Inability or unwillingness to undergo repeated venepuncture (e.g. because of poor tolerability or lack of access to veins)
27. Patients who have received a live vaccine within 4 weeks prior to planned registration must be excluded

Previous exclusion criteria:
Exclusion criteria for Patients with PsA:
1. Active or chronic infection including mycobacterium tuberculosis, HIV, hepatitis B or C , Hep B or C
2. Absence of active psoriatic arthritis
3. Patients who are starting anti-TNF therapy for treating PsA
4. Pregnancy or planning conception or pregnancy. The patient information sheet will state that “if you wish to become pregnant, you need to wait for a minimum of 20 weeks after receiving the last dose of the study medication.”
5. Malignancy
6. Chest X-ray or chest MRI with evidence of ongoing infectious or malignant processobtained within 3 months prior to Screening and evaluated by a qualified physician
7. Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor
8. Patients taking high-potency opioid analgesics (e.g. methadone, hydromorphone, morphine)
9. Use of any investigational drug and/or devices within 4 weeks before randomization or a period of 5 half-lives of the investigational drug, whichever is longer
10. Significant comorbidity that, in the opinion of the investigator, would impact on ability to participate

11. Any change in the dose of oral glucocorticosteroids or DMARDS in the prior 6 weeks prior to the Baseline visit or use of i.v. intramuscular or intra-articular glucocorticosteroid during the last 6 weeks prior to the enrollment visit
12. Patients who have previously been treated with TNFα inhibitors (investigational or approved)
13. History of hypersensitivity to the study drug or its excipients or to drugs of similar classes
14. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 investigational agents (e.g. CAMPATH, anti-CD4, anti-CD5, anti-CD3,anti-CD19)
15. Pregnant or lactating women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test
16. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the entire study or longer if required by locally approved prescribing information
17. Active ongoing inflammatory diseases other than PsA that might confound the evaluation of the benefit of secukinumab therapy
18. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine,cardiac, infectious or gastrointestinal conditions which in the opinion of the Investigator immunocompromise the patient and/or place the patient at unacceptable risk for participation in an immunomodulatory therapy
19. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥ 160/95 mmHg), congestive heart failure (New York Heart Association status of class III or IV), uncontrolled diabetes
20. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFT) such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria:
1. Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out laboratory error.
2. If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed 1.6 mg/dL (27 µmol/L)
21. History of renal trauma, glomerulonephritis, or patients with 1 kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6 µmol/L)
22. Screening total white blood cell (WBC) count < 3 000/µL, or platelets < 100 000/µL or neutrophils < 1 500/µL or hemoglobin < 8.5 g/dL (85 g/L)
23. Active systemic infections during the last 2 weeks (exception: common cold) prior to randomization
24. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5 mm or according to local practice/guidelines) or a positive QuantiFERON TB-Gold test (as indicated in Section 6.5.4 and Table 6-1). Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated
25. Known infection with human immunodeficiency virus, hepatitis B or hepatitis C at Screening or randomization
26. Use of Vitamin D containing supplements

Date of first enrolment

14/10/2016

Date of final enrolment
14/10/2017

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Aintree University Hospital NHS Foundation Trust
Longmoor Lane
Liverpool
United Kingdom
L9 7AL

Sponsor information

Organisation
University of Liverpool

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Industry

Funder Name
Novartis Pharma AG

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository (Liverpool Clinical Trials Units' database)

IPD sharing plan summary

Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results				No	No
HRA research summary			28/06/2023	No	No