Treat to Target trial in axial Spondylo Arthritis :
The TICOSPA (Tight Control in Spondyloarthritis)

Protocol Version 5.0 - December 2016

Protocol n°2016-A00564-47

SPONSOR :
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### Protocol approval page

| Protocol Title: | Treat to Target trial in axial Spondylo Arthritis : The TICOSPA (Tight Control in Spondyloarthritis) |

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<td>Pr Maxime DOUGADOS Signature: date:</td>
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<td>Principal investigator</td>
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1. BACKGROUND

1.1 Spondyloarthritis: the disease at a glance (1)

Spondyloarthritis is the current name given to a disease that can present different clinical features including axial involvement, peripheral rheumatological signs such as enthesitis, arthritis and dactylitis but also extra-rheumatological features such as uveitis, psoriasis, and inflammatory bowel disease. These different signs or symptoms can occur in a same patient concomitantly or subsequently or never...

The axial involvement is the most frequent clinical feature. The usual symptoms consist in inflammatory back pain (e.g. responsible of nocturnal awakenings and morning stiffness). Such symptoms are suggestive of the diagnosis of spondyloarthritis when occurring before the age of 40 or 45 years and are lasting for at least 3 months.

1.2 Diagnosis

The diagnosis is usually made by the physician specialist in rheumatology based on the current symptoms the patient is complaining (e.g. inflammatory back pain) but also based on the interview of the patient with the possibility to detect in the history of the patient and/or his/her family features suggestive of spondyloarthritis. The main investigations helping the physician to make a diagnosis are biologic parameters (CRP, HLA B27) and imaging modalities (pelvic X-Rays permitting to detect structural damage of the sacroiliac joints; MRI of the SIJ permitting to detect subchondral bone edema suggestive of spondyloarthritis).

In clinical studies, a part of the opinion of the rheumatologist, it is usually required that the patient fulfill sets of criteria for such disease. The current validated and accepted criteria are the ones which have been elaborated by ASAS (2).

1.3 Activity of the disease

The concept of “activity” reflects the domain “inflammation”.

Such activity is usually assessed thanks to composite indices such as the BASDAI (3) or the ASDAS (4). The ASDAS has recently shown a better sensitivity to change and a discriminant capacity than other indices (5).
Moreover, for the ASDAS, thresholds permitting to categorize the activity of the disease have been proposed and validated with a score of <1.3 suggesting a remission status, of <2.1 a low disease activity status, and of ≥2.1 an active disease (6) (see Annex I).

### 1.4 Treatment of axial spondyloarthritis

The non-pharmacological interventions such as education, physiotherapy are indicated whatever the stage of the disease.

At variance, the indications of the pharmacological interventions are related to the activity of the disease and also to the potential existence of comorbidities such as mechanical back-pain or fibromyalgia.

The two major pharmacological treatments are Non-Steroidal Anti-inflammatory Drugs (NSAIDs) and Tumor Necrosis Factors blockers. It is usually recommended to evaluate the efficacy of a NSAIDs after 2 to 4 weeks of treatment intake and the TNF blockers after 12 to 16 weeks.

The TNF blockers are only indicated in case of an active disease despite a previous exposure to at least 2 NSAIDs and with the presence of either objective signs of structural damage at pelvic X-Rays or inflammation (e.g. abnormal CRP or abnormal MRI showing subchondral bone edema at the sacroiliac joint level).

The societies ASAS and EULAR have provided recommendations for the management of this disease (7) and ASAS has provided recommendations for the use of TNF-blockers (8).

### 2. TIGHT CONTROL AND TREAT TO TARGET

#### 2.1 The concept

**2.1.1 The tight control** means that as soon as a treatment is initiated in a patient, the time permitting to evaluate its potential efficacy/safety has to be determined. In terms of safety, such time frame can be very short based on the occurrence of adverse events. In terms of efficacy it is usually recommended to evaluate an NSAIDs after 2 to 4 weeks of treatment intake and the TNF blockers after 12 to 16 weeks.
2.2 The evidence

In medicine, there are some areas in which a tight control together with a Treat to Target strategy has demonstrated its benefit in particular in the field of hypertension and diabetes. In the field of rheumatology, such benefit has been demonstrated in rheumatoid arthritis (9) and also at a lower degree of evidence in psoriatic arthritis (10).

2.3 Tight control and Treat to Target in axial spondyloarthritis

To our knowledge, there is no trial that has evaluated the potential benefit of a tight control and a Treat to Target strategy in the field of axial spondyloarthritis (11). However, experts have proposed recommendations in this area (12).

3. OBJECTIVES

To run a strategy trial in order to evaluate the potential benefit of a Treat to Target approach in comparison to routine treatment (i.e. usual care) in patients with axial spondyloarthritis.

3.1 Primary objective:

To compare the percentage of patients with a significant improvement in the ASAS-HI score after a one year follow-up in the 2 groups.

3.2 Secondary objectives:

- To compare the percentage of patients reaching an ASDAS major improvement after a one year follow-up in the 2 groups.
- To compare the percentage of patients reaching an ASDAS clinically important improvement after a one year follow-up in the 2 groups.
- To compare the percentage of patients reaching a BASDAI 50 after a one year follow-up in the 2 groups.
- To compare the change in the ASDAS over one year follow-up in the 2 groups.
To compare the change in the BASDAI over one year follow-up in the 2 groups.

To compare the change in the ASAS-NSAID score over one year follow-up in the 2 groups.

To compare the WPAI after a one year follow-up in the 2 groups.

To compare the EuroQOL after a one year follow-up in the 2 groups.

To compare the self-report questionnaire on health resource utilization after a one year follow-up in the 2 groups.

4. STUDY DESIGN

- Pragmatic, prospective, randomized (cluster)
- Controlled (2 arms), one year duration
- This study is not interventional. This study is reflecting the usual care either in accordance to the treating rheumatologist (arm: usual care) or in accordance to the international scientific recommendations (arm: T2T)
- The randomization by cluster means that in this study this randomization will be done at the investigator level and not at the patient level. This procedure is made in order to prevent any impact of the knowledge of the T2T strategy on the management of the patients enrolled in the usual care arm (13). Therefore, the first step will be to get the consent of the investigators to participate and in particular to be randomized. For the investigators randomized in the usual care arm, there will not be informed of the T2T strategy proposed in this trial until the end of the study.

5. STUDY DURATION

This study will be of one year duration. It seems that this duration will be sufficient to demonstrate a symptomatic benefit of a particular strategy but will be too short to demonstrate a structural effect. Therefore, in this study, only the parameters evaluating the activity of the disease and/or its impact on the quality of life will be collected but not the parameters evaluating the changes in structural damage (e.g. MRI or X-Rays).
6. STUDY ARMS

6.1 Tight control and Treat to Target arm

The treating rheumatologist will agree to monitor very closely (at least every 4 weeks) and also to treat their patients in accordance with a pre-defined strategy (see Annex II).

6.2 Usual care

The treating rheumatologists will continue to manage the enrolled patients in accordance to their usual care.

7. ELIGIBILITY CRITERIA

The eligibility criteria are the following:

- Adults (between 18 and 65 years old)
- With a diagnosis of axial spondyloarthritis according to the axial ASAS criteria AND the opinion of the treating rheumatologist.
- Active disease defined as an ASDAS $\geq 2.1$
- Predominant axial disease meaning that:
  - Patients with non-spinal rheumatological symptoms and/or extra-rheumatological manifestations requiring at baseline the initiation of a specific treatment will be excluded.
  - Patients with a past history and/or a current well controlled non-spinal rheumatological or extra-rheumatological features will be eligible for the study.
- Non-optimally treated with NSAIDs (i.e. who have not received at least 2 NSAIDS, daily during at least 2 weeks at full dose). Annex III summarizes the list of commonly used NSAIDs and the definition of a “full” use.
- With available pelvic X-rays, B27 and MRI of the sacro-iliac joints (performed at any time since symptoms onset)
- With no contraindication to the use of a NSAID
- With no intake of apremilast during the previous 3 months
- Able to understand the objectives of the study and to fill the questionnaires
- Written informed consent.

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It has to be noticed that there is no restriction related to the disease duration.

8. NUMBER OF VISITS

- In the usual care arm, there will be 5 visits (W0, 12, 24, 36 and 48) performed by a research nurse independently to the treating rheumatologist. In this protocol such visits are named “trimestral visits”.
- In the Treat to Target arm, there will be the same trimestral visits plus additional visits at least every 4 weeks performed by the treating rheumatologist (W4, 8, 16, 20, 28, 40 and 44).

9. DATA COLLECTED

9.1 Data collected only at baseline in both groups

- Demographics (age, gender)
- Body Mass Index
- Smoking status
- Educational level
- Disease duration: both the date of the first symptoms suggestive of SpA (and if these symptoms were not related to axial involvement the date of the first axial symptoms). More over the date when the diagnosis has been done will be collected
- Items of the ASAS criteria
- Comorbidities including:
  - Glomerular filtration rate
  - Cardiac status
  - Fibromyalgia according to the FIRST questionnaire (Annex IV).

9.2 Data collected only at baseline only in the tight control

It will be asked to the investigators to screen for tuberculosis, other infections and/or other conditions which might contraindicate or retard the initiation of TNF blockers
9.3 **Data collected every 12 weeks including baseline in both groups**

- ASAS-HI (Annex V)
- ASAS-HI Numerical Rating Sale (Annex VI)
- The five components of the ASDAS (Annex I)
- BASDAI (Annex VII)
- BASFI (Annex VIII)
- WPAI (Annex IX)
- The SpA non axial features (synovitis, dactylitis, enthesitis, uveitis, psoriasis, IBD) according to the ASAS recommendations (Annex X)
- Treatment intake during the last 3 months including NSAIDs (according to the ASAS recommendations (Annex XI)), anti-TNF, analgesics, myorelaxants, antidepressant drugs, physiotherapy.
- The EuroQoL 5 dimension with 5 levels (EQ-5D 5L) questionnaire (Annex XII)
- A self-report questionnaire on health resource utilization (Annex XIII)
- Adverse events (AEs) in the domain of infection, gastro-intestinal, cardio-vascular and allergy

9.4 **Data collected in the Treat to Target arm at all visits**

The 5 components of the ASDAS will be collected and entered immediately (e.g. with the patient still present at the visit) in the e-CRF. Such procedure will permit to the central organization to propose immediately (appearing in the screen of the computer of the investigator) a treatment regimen in accordance to the protocol. Thereafter, the rheumatologist will confirm or not the decision taken concerning the treatment she/ his is indicating to her/ his patient.

10. **SAMPLE SIZE**

10.1 **Primary objective**

The primary objective is to compare the percentage of patients with a significant improvement in the ASAS-HI score after a one year follow-up in the 2 groups.

Based on the current data available and after discussion with Uta KILTZ (in charge of the elaboration and the validation of the ASAS-HI questionnaire) we will consider as a clinically significant
improvement in the ASAS-HI a change of at least 30% after one year of follow-up in comparison to the baseline value.

10.2 Number of patients

We have calculated the sample size in two consecutive steps. In the first one, we have not considered the cluster design (e.g. we have made this calculation with a conventional approach considering that we will randomize the patients).

First step: We anticipate that in the usual care arm there will be 25% of the patients achieving the definition of responders (e.g. ≥30% improvement in the ASAS-HI score after one year of follow-up). Considering the following risks (α =5% and β =80%) and a bilateral test, we will need 77 patients per arm to demonstrate a difference of 20% in the percentage of responders (e.g. we will consider as a positive trial if the percentage of patients achieving the definition of responders (e.g. ≥30% improvement in the ASAS-HI score after one year of follow-up) be at least 45% in the T2T arm in case we will observe 25% responder rate in the usual arm.

Second step: we have considered the cluster design by multiplying such number by an “inflation factor” defined as $1 + (m-1)\times p$ where $m$ is equal to the size of the cluster (in our study 10 = number of patients per center) and $p = 0.05$ (e.g. 1.45 for our study).

In order to uniformize the number of patient per center, we need to get a round figure and therefore we will include 160 patients (80 patients per arm).

10.3 Number of patients per center

We anticipate that each participating center will be able to recruit 10 patients within one year. The recruitment will be competitive but will not accept more than 20 patients per center.

11. STUDY DRUGS

The choice of the drugs necessary to the patients (e.g. analgesics, NSAIDs, biologics,..) is at the discretion of the treating rheumatologist based on the characteristics of the patients and the experience of the rheumatologist.

12. SAFETY

An adverse event is defined as: “Any untoward medical occurrence in a patient administered the drug of interest and which does not necessarily have a causal relationship with the treatment.”
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For this study, all adverse events (AEs) experienced by patients in the domain of infection, gastro-intestinal, cardio-vascular and allergy, during their participation in the study have to be collected and recorded in the case report form. This data will be collected according to the EULAR Recommendations for collecting comorbidities (REF: Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. Baillet A, Gossec L, Carmona L, Wit Md, van Eijk-Hustings Y, Bertheussen H, Alison K, Toft M, Kouloumas M, Ferreira RJ, Oliver S, Rubbert-Roth A, van Assen S, Dixon WG, Finckh A, Zink A, Kremer J, Kvien TK, Nurmohamed M, van der Heijde D, Dougados M. Ann Rheum Dis. 2016 Jun;75(6):965-73. doi: 10.1136/annrheumdis-2016-209233)

The investigators will be responsible for reporting all other AEs and serious AEs possibly related to treatment according to the local regulations.

13. LOGISTICS

13.1 Steering committee

- The principal investigator is Maxime Dougados
- The scientific steering committee comprises 4 members: Desirée van der Heijde, Filip van den Bosch, Joachim Sieper and Maxime Dougados
- The international study coordinator is Anna Moltó
- The biostatistician is Adrien Etcheto

13.2 Participating countries

Three countries are participating:
- Belgium
- France
- The Netherlands

13.3 Participating centers

The invitation/selection of the participating centers is under the responsibility of the steering committee members (e.g. Désirée van der Heijde for the Netherlands, Filip van den Bosch for Belgium and Maxime Dougados for France).

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There will be 4 centers in the Netherlands, 4 centers in Belgium and 10 centers in France.

13.4 Good clinical Practices

This study will be conducted in accordance with the current Good Clinical Practices in each participating country.

13.5 e-CRF

The CRF will be an e-CRF supplied by the CRO. The system used is validated and complies with 21 CFR Part 11. Individual, personalized identifiers will be handed to the investigators to access the eCRF. These identifiers are strictly confidential.

The patient data collected in the eCRF will be documented in a confidential manner, by coding it without any mention to the first and last names. The patient will be identified by a number only. The database created for the analysis will therefore contain no means by which to identify the patients. Each physician is responsible for establishing and regularly maintaining an up-to-date, confidential list allowing identification of a patient and his/her corresponding study number, for purposes of verifying source data.

The patient’s dossier containing the source data guarantees the patient’s existence and the integrity of the data collected.

Data entry will be performed directly by the participating physicians on the secure internet site. It will automatically feed the study’s database. The database will be backed up electronically every day. Key data will be made compulsory in the eCRF in order to manage the proportion of missing data.

Automatic consistency checks will be set up in the eCRF so that the investigator can be guided when entering data and make corrections where there are any errors. These checks are made in particular on the format of data entered, missing data, outliers and inter-field inconsistencies.

For the e-CRF, the organization will be different for the trimestral visits (both groups) and the intermediate visits (T2T arm).

13.5.1 CRF for the trimestral visits
There will be a paper form of the CRF with patient’s questionnaires in the local language. Thereafter, each participating center will have to enter the collected data in a e-CRF in which the information will be only in English. The data entry of this CRF can be done either at the time of the visit (e.g. the patient still physically present) or several days later but never more than 10 days after the visit.

13.5.2 CRF for the intermediate visits in the T2T arm.

Such CRF will be ONLY e-CRF, it will have to be filled in by the investigator in presence of the patient (see section 8.d. of the present protocol).

13.6 Monitoring

PSNRESEARCH has been chosen as the CRO in charge of this study.

The task of the CRO will be to be in charge of:

- Checking that the proposed study is in accordance with the Good Clinical Practices
- Facilitating the liaison of the principal investigators(s) and the different bodies (e.g. ethical committee, national agencies,...)
- Elaboration of the paper and the e-CRF in collaboration with the steering committee
- Financial contracts with the centers
- Opening of the centers
- Definition of queries and management of such queries
- Monthly report of the enrollment of the patients and eventually description of issues during the study.

13.7 Randomization and kick-off meeting

After consent of an investigator to participate at the study, she/he will be randomly allocated to one of the 2 arms.

In case she/he is allocated to the usual care arm she/he will be invited to participate at a kick-off meeting (potentially only the research nurse of the center will attend this meeting). During this meeting, the main objectives of the trial will be explained BUT the Tight Control and the proposed treatment strategy will not be revealed.
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In case she/he is allocated to the T2T arm she/he will be invited to participate (mandatory presence of the investigator and her/his research nurse) at a different kick-off meeting during which both the main objectives of the trial and the detailed proposed treatment strategy will be presented.

14. TIMING

It is anticipated the following:

- Kick-off meetings: Fall 2016
- First patient In in November 2016
- Last patient In in November 2017
- First patient Out in November 2017
- Last patient Out in November 2018
- Lock of the database in January 2019
- Preparation of the abstracts to international congresses and the main manuscript to the finalized by June 2019
- Presentation of the results to all the participants at the meeting September 2019
15. REFERENCES


8. van der Heijde D, Sieper J, Maksymowych WP, Dougados M, Burgos-Vargas R, Landewé R, Rudwaleit M, Braun J; Assessment of SpondyloArthritis international Society. 2010 Update of
A.R.C.R


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16. ANNEXES

Annex I: ASDAS Index
Annex II: Proposed Tight control and Treat to Target strategy in axial SpA
Annex III: Definition of “full” dose of NSAIDs
Annex IV: Fibromyalgia Rapid Screen Tool (FIRST)
Annex V: ASAS-HI
Annex VI: ASAS-HI Numerical Rating Scale
Annex VII: BASDAI
Annex VIII: BASFI
Annex IX: WPAI
Annex X: ASAS recommendations for collecting clinical features of spondyloarthritis
Annex XI: ASAS recommendations for collecting NSAID intake in Spondyloarthritis
Annex XII: EuroQol 5 dimension with 5 levels (EQ-5D 5L) questionnaire
Annex XIII: Self-report questionnaire on health resource utilization
Annex I: ASDAS index

**ASDAS**
Ankylosing Spondylitis Disease Activity Score

<table>
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<tr>
<th>Back Pain [0-10]</th>
<th>Morning Stiffness [0-10]</th>
<th>Patient Global [0-10]</th>
<th>Peripheral Pain/Swelling [0-10]</th>
<th>C-Reactive Protein (mg/l)</th>
<th>Erythrocyte Sedimentation Rate (mm/hr)</th>
<th>ASDAS-CRP</th>
<th>ASDAS-ESR</th>
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**ASDAS**

<table>
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<tr>
<th>Disease</th>
<th>Activity</th>
<th>Status</th>
<th>ASDAS Criteria</th>
<th>Improvement</th>
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<tbody>
<tr>
<td>&lt; 1.3</td>
<td></td>
<td></td>
<td>Δ ≤ 1.1</td>
<td>Clinically Important Improvement</td>
</tr>
<tr>
<td>1.3 ≤ 2.1</td>
<td></td>
<td></td>
<td></td>
<td>Major Improvement</td>
</tr>
<tr>
<td>&gt; 2.1</td>
<td></td>
<td></td>
<td>Δ ≥ 2.0</td>
<td></td>
</tr>
<tr>
<td>&gt; 3.5</td>
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A CRP value <2mg/l is not allowed. If the conventional CRP is below the limit of detection or if the high sensitivity CRP is <0.5mg/l, the constant value of 2mg/l should be used.
Proposed Tight Control and Treat to Target strategy in axial SpA

1. **Time frame of the visits**
   
   It is anticipated that the patients will be monitored every 4 weeks as soon as the ASDAS is above 1.3.
   
   In case of 2 consecutive visits with an ASDAS <1.3 AND no decision to change therapy at this latter visit, the patient can be contacted over the phone.

2. **Treatments considered**
   
   A part from the 3 “cornerstone” therapies (e.g. physiotherapy, NSAIDs, anti-TNF) we will also consider the possibility of other therapeutic modalities such as analgesics, myorelaxants,…
   
   Concerning the physiotherapy, it is considered that such treatment is always indicated for all the patients during the entire duration of the trial. The exact treatment regimen (e.g. home exercises, supervision by a physiotherapist,...) will be based on the local/national procedures and will not be detailed here.

3. **Definition of the target**
   
   The Target will be defined by an ASDAS score<2.1. In case the CRP will be not evaluated every 4 weeks, the last available CRP will be used for the calculation of the ASDAS.

4. **The different therapeutical steps**
   
   For each step, we will define
   
   - The indications
   - The proposed treatment
   - The time of the outcome to be assessed
   - The outcome

   We are anticipating the following consecutive steps in case of insufficient efficacy:

   - STEP 1: FIRST NSAID
   - STEP 2: SECOND NSAID
   - STEP 3: FIRST ANTI-TNF
   - STEP 4: SECOND ANTI-TNF
   - STEP 5: THIRD ANTI-TNF OR OTHER AVAILABLE BIOLOGICS
5. Detailed description of each step

**STEP 1 = FIRST NSAIDs**
- **Indications**: Inclusion criteria of the study fulfilled and in particular ASDAS>2.1
- **Treatment**: First NSAIDs, full dose, daily
- **Time to the outcome to be assessed**: 2 to 4 weeks
- **Outcome**:
  - ASDAS <1.3 ⇒ taper (or continue based on a shared decision)
  - ASDAS≥1.3 and <2.1 ⇒ continue (or step 2 or taper based on a shared decision)
  - ASDAS≥2.1 or intolerance ⇒ step 2.

**STEP 2 = SECOND NSAIDs**
- **Indications**: Intolerance to the previous NSAIDs OR ASDAS >2.1 despite the previous NSAIDs intake OR ASDAS≥1.3 and <2.1 despite the previous intake but decision to go to step 2 based on a shared decision
- **Treatment**: Second NSAIDs full dose
- **Time to the outcome to be assessed**: 2 to 4 weeks
- **Outcome**:
  - ASDAS <1.3 ⇒ taper (or continue based on a shared decision)
  - ASDAS≥1.3 and <2.1 ⇒ continue (or step 3 or taper based on a shared decision)
  - ASDAS≥2.1 or intolerance ⇒ step 3
  - Intolerance to the 2 evaluated NSAIDs ⇒ step 3
  - Intolerance to only one of the 2 evaluated NSAIDs ⇒ step 2B

**STEP 2B : THIRD NSAIDs**
- **Indications**: Intolerance to only one of the 2 previously evaluated NSAIDs
- **Treatment**: Third NSAIDs, full dose, daily
- **Time to the outcome to be assessed**: 2 to 4 weeks
- **Outcome**:
  - ASDAS <1.3 ⇒ taper (or continue based on a shared decision)
  - ASDAS≥1.3 and <2.1 ⇒ continue (or taper based on a shared decision)
  - ASDAS≥2.1 ⇒ step 3
  - Intolerance ⇒ step 3
A.R.C.R

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STEP 3: POTENTIAL INDICATION OF THE FIRST ANTI-TNF

ASDAS

<2.1

≥2.1

AND

Insufficient efficacy or intolerance of NSAIDs after the first two steps

AND

Abnormal CRP or Abnormal MRI or Abnormal X-Rays

AND

No contra-indication to anti-TNF

NO

YES

STEP 3 A

Protocol Version 5.0—December 2016

24
STEP 3 A: FIRST ANTI-TNF

- **Indications**: Intolerance or insufficient efficacy of 2 previously evaluated NSAID AND ASDAS ≥2.1 AND at least one of the following abnormalities: abnormal CRP (<3 months), abnormal MRI (<X months), abnormal X-Rays (ever) AND in accordance with local TNFi indication/reimbursement guidelines
- **Treatment**: First anti-TNF
- **Time to the outcome to be assessed**: 12 weeks
- **Outcome**:
  - ASDAS <1.3 ⇒ continue anti-TNF and taper NSAIDs (or continue same NSAIDs regimen based on a shared decision)
  - ASDAS≥1.3 and <2.1 ⇒ continue both anti-TNF and NSAIDs (or taper NSAIDs based on a shared decision)
  - ASDAS≥2.1 and Δ ASDAS ≥1.1
    ⇒ continue the same treatment for 4 weeks
  - ASDAS≥2.1 and Δ ASDAS < 1.1
    ⇒ stop anti-TNF and go to step 4
  - Intolerance ⇒ stop anti-TNF and go to step 4

STEP 3 B

- **Indications**: Intolerance or insufficient efficacy of 2 previously evaluated NSAIDs AND ASDAS ≥2.1 AND either ASDAS <2.1 or (normal CRP, normal MRI and normal X-Rays)
- **Treatment**: Intensification of physiotherapy and/or new NSAIDs and/or analgesics and/or myorelaxants and/or...
- **Time to the outcome to be assessed**: 4 weeks
- **Outcome**:
  - ASDAS <1.3 ⇒ taper the ongoing treatments (or continue based on a shared decision)
  - ASDAS≥1.3 and <2.1 ⇒ continue (or taper or go back to step 3 based on a shared decision and/or new data (e.g. abnormal CRP or abnormal MRI or abnormal X-Rays)
  - ASDAS≥2.1 ⇒ go back to step 3
**STEP 4: POTENTIAL INDICATION OF A SECOND ANTI-TNF**

- **Unacceptable tolerability of the previous anti-TNF**
  - **YES**
  - **NO**

- **STEP 4 A**
  - **Insufficient efficacy of the previous anti-TNF**
    - **ASDAS \( \geq 2.1 \)**
      - **YES**
      - **NO**

- **Pain related to SpA**
  - **YES**
  - **NO**

- **STEP 4 B**
  - **STEP 4 C**
STEP 4 A : Unacceptable tolerability of the first anti-TNF

- Indications : Intolerance of the first anti-TNF
- Treatment : Stop anti-TNF
- Time to the outcome to be assessed : 4 weeks or more frequently if necessary
- Outcome:
  - Intolerance resolved ⇒ go back to step 4 considering the absence of intolerance (e.g. Step 4 B or 4 C)
  - Intolerance unresolved ⇒ continue the management of the adverse event and go to Step 3 B.

STEP 4 B : INDICATIONS OF A SECOND ANTI-TNF

- Indications : ASDAS≥2.1 after 12 or 16 weeks of the first anti-TNF AND pain considered as related to SpA AND in accordance with local TNFi indication/reimbursement guidelines
- Treatment : Second anti-TNF
- Time to the outcome to be assessed : 12 weeks
- Outcome:
  - ASDAS <1.3 ⇒ continue anti-TNF and taper NSAIDs (or continue same NSAIDs regimen based on a shared decision)
  - ASDAS≥1.3 and <2.1 ⇒ continue both anti-TNF an NSAIDs (or taper NSAIDs based on a shared decision)
  - ASDAS≥2.1 and Δ ASDAS ≥1.1 ⇒ continue the same treatment for 4 weeks
  - ASDAS≥2.1 and Δ ASDAS < 1.1 ⇒ stop anti-TNF and go to step 5
  - Intolerance ⇒ stop anti-TNF and go to step 5
STEP 4 C: DOUBT ON THE INDICATION OF A SECOND ANTI-TNF

- **Indications:**
  - ASDAS≥2.1 after 12 or 16 weeks of the first anti-TNF AND pain considered as not related to SpA
  - ASDAS<2.1 after 12 or 16 weeks of the first anti-TNF
- **Treatment:** Stop anti-TNF
- **Time to the outcome to be assessed:** 4 weeks
- **Outcome:**
  - Δ ASDAS≥1.1 (flare) AND in agreement with reimbursement ⇒ step 5
  - Δ ASDAS<1.1 (no flare) ⇒ step 3 B

STEP 5: POTENTIAL INDICATION OF A THIRD ANTI-TNF (or another biotherapy if available)

- **Indications:**
  - Failure of the second anti-TNF according to the definition given in Step 4 B
  - Flare after discontinuation of the second anti-TNF and in agreement with reimbursement.
- **Treatment:** Third anti-TNF or another biotherapy such as anti-IL17 inhibition if available.
- **Time to the outcome to be assessed:** 12 weeks
- **Outcome:**
  - ASDAS <1.3 ⇒ continue anti-TNF and taper NSAID (or continue same NSAID regimen based on a shared decision)
  - ASDAS≥1.3 and <2.1 ⇒ continue both anti-TNF an NSAIDs (or taper NSAIDs based on a shared decision)
  - ASDAS≥2.1 and Δ ASDAS ≥1.1
    ⇒ continue the same treatment for 4 weeks
  - ASDAS≥2.1 and Δ ASDAS < 1.1
    ⇒ stop anti-TNF and go to step 4 B or C
  - Intolerance ⇒ stop anti-TNF and go to step 4A
Annex III: Definition of “full” dose of NSAIDs*

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Dose/mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>150</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1000</td>
</tr>
<tr>
<td>Aceclofenac</td>
<td>200</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>400</td>
</tr>
<tr>
<td>Etodolac</td>
<td>600</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>120</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>300</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>2400</td>
</tr>
<tr>
<td>Indometacin</td>
<td>150</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>200</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>15</td>
</tr>
<tr>
<td>Nimesuline</td>
<td>200</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>400</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>20</td>
</tr>
<tr>
<td>Tenoxicam</td>
<td>25</td>
</tr>
</tbody>
</table>

Annex IV: The Fibromyalgia Raid screening Tool (FiRST)*

Yes  No

I have pain all over my body
My pain is accompanied by a continuous and very unpleasant general fatigue
My pain feels like burns, electric shocks or cramps
My pain is accompanied by other unusual sensations throughout my body, such as pins and needles, tingling or numbness
My pain is accompanied by other health problems such as digestive problems, urinary problems, headaches or restless legs
My pain has a significant impact on my life, particularly on my sleep and my ability to concentrate, making me feel slower generally

Annex V : ASAS Health Index

Please answer all statements by placing one check mark per statement to indicate which response best applies to you at this moment in time taking into account your rheumatic disease (the term “rheumatic disease” contains all forms of spondyloarthritis including ankylosing spondylitis).

1. Pain sometimes disrupts my normal activities.
2. I find it hard to stand for long.
3. I have problems running.
4. I have problems using toilet facilities.
5. I am often exhausted.
6. I am less motivated to do anything that requires physical effort.
7. I have lost interest in sex.
8. I have difficulty operating the pedals in my car.
9. I am finding it hard to make contact with people.
10. I am not able to walk outdoors on flat ground.
11. I find it hard to concentrate.
12. I am restricted in traveling because of my mobility.
13. I often get frustrated.
14. I find it difficult to wash my hair.
15. I have experienced financial changes because of my rheumatic disease.
16. I sleep badly at night.
17. I cannot overcome my difficulties.

For each of these questions the answer can be either “I agree” or I do not agree” or (for question#7 “Not applicable,” I do not want to answer”) or for question#8 “Not applicable,” I cannot / do not drive”).

Annex VI: ASAS Health Index numerical rating scale

For each of the 17 questions, the modality of the answer will be the one proposed by the original publication (e.g. binary variable), moreover in this study we will add the following:

“In case you answered “I agree” what is the level of discomfort you had during the last 48 hours from 0=nil to 10 = extreme
Annex VII: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)*

Please place a vertical mark on each line below that best describes your answer to each question, relating to the last 48 hours.

1. How would you describe the overall level of fatigue/tiredness you have experienced?
   None 0 1 2 3 4 5 6 7 8 9 10 Very severe

2. How would you describe the overall level of AS neck, back or hip pain you have had?
   None 0 1 2 3 4 5 6 7 8 9 10 Very severe

3. How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?
   None 0 1 2 3 4 5 6 7 8 9 10 Very severe

4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?
   None 0 1 2 3 4 5 6 7 8 9 10 Very severe

5. How would you describe the overall level of morning stiffness you have had from the time you wake up?
   None 0 1 2 3 4 5 6 7 8 9 10 Very severe

6. How long does your morning stiffness last from the time you wake up? I___I___I___I minutes

Annex VIII: Bath Ankylosing Spondylitis Functional Index (BASFI)*

Please place a vertical mark on each line below that best describes your level of ability with each of the following activities during the last 48 hours: (an aid is a piece of equipment which helps you to perform and action or movement).

1. Putting on your socks or tights without help or aids (e.g. sock aid)
   Easy 0 1 2 3 4 5 6 7 8 9 10 Impossible

2. Bending forward from the waist to pick up a pen from the floor without an aid
   Easy 0 1 2 3 4 5 6 7 8 9 10 Impossible

3. Reaching up to a high shelf without help or aids (e.g. helping hand)
   Easy 0 1 2 3 4 5 6 7 8 9 10 Impossible

4. Getting up out of an armless dining room chair without using your hands or any other help
   Easy 0 1 2 3 4 5 6 7 8 9 10 Impossible

5. Getting up off the floor without help from lying in your back
   Easy 0 1 2 3 4 5 6 7 8 9 10 Impossible

6. Standing unsupported for 10 minutes without discomfort
   Easy 0 1 2 3 4 5 6 7 8 9 10 Impossible

7. Climbing 12-15 steps without using a handrail or walking aid. One foot on each step
   Easy 0 1 2 3 4 5 6 7 8 9 10 Impossible

8. Looking over your shoulder without turning your body.
   Easy 0 1 2 3 4 5 6 7 8 9 10 Impossible

9. Doing physically demanding activities (e.g. physiotherapy exercises, gardening or sports)
   Easy 0 1 2 3 4 5 6 7 8 9 10 Impossible

10. Doing a full day’s activities whether it be at home or at work
    Easy 0 1 2 3 4 5 6 7 8 9 10 Impossible

Annex IX: Work status WPAI*

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. Please fill in the blanks or circle a number, as indicated.

1. Are you currently employed (working for pay)?
   - Yes
   - No
   If NO check “NO“ and skip to question 6.

The next questions refer to the past seven days, not including today:

2. During the past seven days, how many hours did you miss from work because of your health problems? Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.
   - Hours

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?
   - Hours

4. During the past seven days, how many hours did you actually work?
   - If “0”, check “0” and skip to question 6.
   - Hours

5. During the past seven days, how much did your health problems affect your productivity while you were working? Think about days you were limited in the amount or kind of work you would do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

<table>
<thead>
<tr>
<th>Health problems had no effect on my work</th>
<th>Health problems completely prevented me from working</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

CIRCLE A NUMBER!

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities (other than work at a job)? By regular activities, we mean the usual activities you do, such as work around the house, shopping, child care, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

<table>
<thead>
<tr>
<th>Health problems had no effect on my daily activities</th>
<th>Health problems completely prevented me from doing my daily activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

CIRCLE A NUMBER!


Annex X: ASAS recommendations for collecting clinical features of spondyloarthritis

Protocol Version 5.0–December 2016
Uveitis  ASAS recommendations for collecting the information related to uveitis in longitudinal studies of spondyloarthritis, in which uveitis is not the primary clinical feature of interest.

**Acute anterior uveitis** (e.g. diagnosis of uveitis by an ophthalmologist OR an episode suggestive of uveitis in a patient with a previous history of an episode diagnosed as uveitis by an ophthalmologist).

a. Such diagnosis (tick only one box)  
- has never been made  
- was known at the precedent visit  
- has been made since the last visit  

b. If a diagnosis of uveitis has been made, thanks to answer to the following:
   - Number of episodes since the last visit /___/___/  
   - treatment received for at least one episode yes no  
     - None .................................................................  
     - Drops of corticosteroids ................................  
     - Local injection of steroids ................................  
     - Systemic administration of steroids ..................

Inflammatory Bowel disease  ASAS recommendations for collecting the information related to inflammatory bowel disease (IBD) in longitudinal studies of spondyloarthritis, in which IBD is not the primary clinical feature of interest.

**Inflammatory bowel disease** (e.g. past or present Crohn’s disease or ulcerative colitis diagnosed by a gastroenterologist)

a. Such diagnosis (tick only one box)  
- has never been made  
- was known at the precedent visit  
- has been made since the last visit  

If yes, which one yes no  
- Crohn’s disease ..................................................  
- Ulcerative colitis ..................................................  
- Other .................................................................  
- If yes, precise .........................................................

b. Specific treatment for IBD since the last visit  

Psoriasis  ASAS recommendations for collecting the information related to psoriasis in longitudinal studies of spondyloarthritis, in which psoriasis is not the primary clinical feature of interest.

**Psoriasis** (e.g. skin and/or nail lesions diagnosed as psoriasis by a physician)

a. Such diagnosis (tick only one box)  
- has never been made  
- was known at the precedent visit  
- has been made since the last visit  

b. Current status  
   - % skin area with psoriasis* /___/___/___/  
     *(1%) = palm of hand – if no psoriasis, note /0_/0_/0_/0_/  
   - Specific treatment for psoriasis since the last visit Yes  

Peripheral arthritis  ASAS recommendations for the technique of collecting the information related to peripheral arthritis in longitudinal studies of spondyloarthritis, in which peripheral arthritis is not of primary interest.
Peripheral joint involvement

Did the patient complain from any sign/symptom suggestive of peripheral articular involvement since the last visit? ................. Yes □ No □
⇒ If yes please complete the 2 following mannequins regarding the tender and swollen joints

Swollen joint count (44)

Tender joint count (44)

Dactylitis: ASAS recommendations for the technique of collecting the information related to dactylitis in longitudinal studies of spondyloarthritis in which dactylitis is not of primary interest.

Dactylitis: Did the patient complain or is complaining from any sign/symptom suggestive of dactylitis since the last visit? ................. Yes □ No □
⇒ If yes, complete the following (all that apply)

Finger

<table>
<thead>
<tr>
<th></th>
<th>left</th>
<th>right</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>II</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>III</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>IV</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>V</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

Toe

<table>
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<th>right</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
Enthesitis: ASAS recommendations for collecting the information related to enthesitis in longitudinal studies of spondyloarthritis, in which enthesitis is not the primary clinical feature of interest.

Did the patient complain for any sign, symptom suggestive of enthesitis? ...... Yes □ No □
⇒ If yes, please refer to any enthesitis scoring system

ASAS recommendations for variables to be collected in clinical trials/epidemiological studies of spondyloarthritis.

**Annex XI – ASAS recommendations for collecting NSAID intake in spondyloarthritis**

<table>
<thead>
<tr>
<th>NSAID name</th>
<th>Average daily dose intake</th>
<th>Days with intake</th>
<th>Starting date</th>
<th>Ending date</th>
</tr>
</thead>
<tbody>
<tr>
<td>...............</td>
<td>mg</td>
<td>&lt; 1 day/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 to 3 days/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 to 5 days/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 5 days/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Every day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ASAS** recommendations for collecting, analysing and reporting NSAID intake in clinical trials/epidemiological studies in axial spondyloarthritis.

**Dougados** M., Simon P., Braun J., Burgos-Vargas R., Maksymowych W.P., Sieper J., van der Heijde D.

Ann Rheum Dis. 2011 Feb;70(2):249-51
Annex XII - EuroQoL 5 dimension with 5 levels (EQ-5D 5L) questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY.

**MOBILITY**
- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

**SELF-CARE**
- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

**USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)**
- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

**PAIN / DISCOMFORT**
- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

**ANXIETY / DEPRESSION**
- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed
Annex XIII - Self-report questionnaire on health resource utilization

Questions about your use of health care
in the last 3 months

Please note, we aim to register all your health care utilization, and not only the health care use related to your rheumatic disease. Also, healthcare visits/use as part of this study should be taken into account.

Question 1. How many appointments did you have in the last 3 months with each of the following health care providers? Only actual visits count, not phone calls with professionals for various reasons

<table>
<thead>
<tr>
<th>Type of health care professional</th>
<th>How often did you visit in the last three months this doctor/health care professional? (Please fill in '0' if you did not visit this professional in the last 3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example cardiologist</td>
<td>example 2 times</td>
</tr>
<tr>
<td>huisarts</td>
<td>...... times</td>
</tr>
<tr>
<td>reumatoog</td>
<td>... times</td>
</tr>
<tr>
<td>arts eerste hulp (spoedgevallen)</td>
<td>... times</td>
</tr>
<tr>
<td>andere specialist</td>
<td>... times</td>
</tr>
<tr>
<td>gespecialiseerde verpleegkundige</td>
<td>... times</td>
</tr>
<tr>
<td>fysiotherapeut</td>
<td>... times</td>
</tr>
<tr>
<td>andere*:</td>
<td>... times</td>
</tr>
</tbody>
</table>

*: such as a psychologist, chiropractor, medical dietician, medical podologist

Please do NOT mention alternative health care providers (acupuncturist, homeopath, etc)
A.R.C.R                                     TICOSPA (A.R.C.R.-2016-3.2)

Question 2. How often in the past 3 months did you stay in hospital day care for a treatment or procedure (at least several hours)? You did not stay overnight. For example, you came for a blood transfusion, infusion of biological, rehabilitation therapy, pain treatment, dialysis, etc.

<table>
<thead>
<tr>
<th>Type of day care treatment/procedure</th>
<th>How many times in the past 3 months did you have to attend the daycare for such a treatment/procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>example blood transfusion</td>
<td>example 2 times</td>
</tr>
<tr>
<td>Infusion of biologic (infliximab, abatacept, ...)</td>
<td>... times</td>
</tr>
<tr>
<td>rehabilitation day care</td>
<td>... times</td>
</tr>
<tr>
<td>other: ........................................</td>
<td>... times</td>
</tr>
</tbody>
</table>

Question 3. How many days in the past 3 months did you stay in a hospital? You stayed overnight.

<table>
<thead>
<tr>
<th>Type of hospital</th>
<th>How many days in the past 3 months did you had to stay in a hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>example psychiatric hospital</td>
<td>example 2 days</td>
</tr>
<tr>
<td>hospital</td>
<td>... days</td>
</tr>
<tr>
<td>rehabilitation center</td>
<td>... days</td>
</tr>
<tr>
<td>nursing home</td>
<td>... days</td>
</tr>
<tr>
<td>other: .....................................</td>
<td>... days</td>
</tr>
</tbody>
</table>

Question 4. Do you have paid work? [ ] Yes [ ] No

If yes, how many working days did you miss from your paid work in the last 3 months due to your health. Caution (1) if you missed half a day, count than as a half day! (2) Fill in ‘0’, if you did not miss any working day.

_____ , ____ working days

THANKS FOR COMPLETING THIS QUESTIONNAIRE