Supplementary documentation AGIL-CV to record cardiovascular and metabolic risk factors in RA patients treated with adalimumab in routine clinical practice

Amendment I (dated 06-Mar-2012) of the observational plan AGIL GER 08-05 (17-May-2010)

This non-interventional study is to be conducted according to this observational plan. [redacted]

Table of contents

1 Changes to the observational plan 4
1.1 Introduction 4
1.2 Rationale 5
1.3 Research question 5
1.5 Physician's selection criteria AGIL-CL 6
1.6 Course of long-term AGIL-CV documentation 6
1.7 Description of study activities 8
1.8 Calculation of CV risk model 9
1.9 Sample size estimation 10
1.10 Biometrics concept of AGIL-CV 11
1.11 Time points of statistical analysis 11
1.12 References 12

Abbreviations and Definitions

Extension of the list of AGIL abbreviations:

dcrit	Critical difference
ESCCA	EULAR Standing Committee for Clinical Affairs
EULAR	European League Against Rheumatism
HDL cholesterol	High-density lipoprotein cholesterol
LDL cholesterol	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
SCORE	Systematic Coronary Risk Evaluation

1 Changes to the observational plan

1.1 Introduction

Introduction: AGIL-CV as a supplement to AGIL:

Amendment I describes the collection and analysis of cardiovascular and metabolic risk parameters in patients with rheumatoid arthritis (RA) determined in the course of additional documentation to NIS AGIL.

RA patients have increased cardiovascular morbidity and mortality as compared to the overall population. Furthermore, the majority of premature deaths in RA patients are attributable to cardiovascular disease (1), (2). RA patients show a higher cardiovascular risk, which can be put down to a higher prevalence of traditional risk factors (e.g. hypertension, dyslipidemia, smoking (3) as well as the underlying systemic inflammation, which play a key role in the development and progression of arteriosclerosis (4). Markers of inflammation are independent predictors of cardiovascular death (5). The systemic inflammation may even be the key process leading to myocardial infarction and premature death (6). RA is also associated with a pro-atherogenic lipid profile: Low HDL cholesterol levels are observed, which lead to an unfavorable cholesterol ratio (total cholesterol/HDL cholesterol) (7), (8). The prevalence of cardiovascular disease in RA is increased to an extent that is comparable to that of type 2 diabetes (9). Accordingly, RA should be regarded as an independent cardiovascular risk factor, and regular cardiovascular risk screening and management is therefore needed (1).

As TNF plays a significant role in the development of inflammatory processes, the inflammatory process of arteriosclerosis may be interrupted by inhibiting this cytokine. Studies show that early initiation of effective therapy is associated with a decreased cardiovascular risk (6), (10), (11).

The Standing Committee for Clinical Affairs of the European League Against Rheumatism ([EULAR], ESCCA) thus issued evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis that stress the implication of adequate control of disease activity and annual examinations to assess the cardiovascular risk (1).

Rheumatologists implementing these recommendations in everyday practice can routinely record their RA patients' cardiovascular and metabolic risks using this documentation.

1.2 Rationale

Rationale and considerations regarding objectives of AGIL-CV in addition to AGIL:

This supplementary documentation serves to record cardiovascular and metabolic risk factors in RA patients prior to starting adalimumab treatment in a routine clinical setting. In addition, the course of these risk factors and the impact of the disease activity on this course are to be documented during the 60-month adalimumab treatment.

1.3 Research question

Description of study aims AGIL-CV as a supplement to AGIL:

The **primary research questions of AGIL-CV** are

- To determine baseline changes in Months 12, 24 and 60 after starting adalimumab treatment with regard to the following primary cardiovascular and metabolic parameters:
    - Lab chemistry blood parameters for glucose and lipid metabolism
    - Vital signs
    - Body measurements
- The comparison between DAS28 responders and DAS28 nonresponders in terms of the primary parameters "lab chemistry blood parameters for glucose and lipid metabolism" and "vital signs"
- Determination of the time point and frequency of cardiovascular events in the course of the entire documentation

The secondary **research question** addresses the investigation of the impact of the

personal data and familial medical history recorded at baseline on the previously specified cardiovascular and metabolic parameters. The Systematic Coronary Risk Evaluation (SCORE) risk model is applied to determine the individual risk and changes thereof over time.

1.4 Number of patients to be included in AGIL-CV

Patient number required for the AGIL-CV research question in addition to AGIL

At least N=300 RA patients are required for the study to evaluate the cardiovascular and metabolic changes. This number takes premature therapy discontinuation by 50% of patients up to Month 60 into account (see Section 1.9).

1.5 Physician's selection criteria AGIL-CL

Additional selection criteria for the conduct of AGIL-CV:

The data for additional documentation of cardiovascular and metabolic risk factors are collected at selected sites that determine the cardiovascular risk profile as a routine measure for monitoring RA patients. All of these sites participate in NIS AGIL.

1.6 Course of long-term AGIL-CV documentation

Additional supplement of AGIL-CV:

This non-interventional study **(including Amendment I)** is conducted as a single-arm, multi-center, prospective cohort study.

Table 1 "Physician's overview" is supplemented by the following sub-table that shows the process of medical documentation for AGIL-CV.

Table 1 Physician's overview – collection of cardiovascular and metabolic risk factors

	Month							
	0	**3**	**6**	**12**	**24**	**36**	**48**	**60[1]**
Body measurements (weight, height, waist and hip circumference) [2]	X	X	X	X	X	X	X	X
Familial medical history (diabetes, obesity, premature cardiovascular disease)	X							
Tobacco use	X	X	X	X	X	X	X	X
Alcohol consumption	X	X	X	X	X	X	X	X
Vital signs [3]	X	X	X	X	X	X	X	X
Documentation of cardiovascular events (myocardial infarction, stroke)	X	X	X	X	X	X	X	X
Laboratory parameters (fasted) [3,4]	X	X	X	X	X	X	X	X

[1] Month 60 or last visit
[2] Height is only determined at Month 0.
[3] Data are incorporated into the SCORE risk model.
[4] Glucose (serum or plasma), lipid profile (HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides, CRP)

1.7 Description of study activities

Description of data to be documented for AGIL-CV as a supplement to AGIL:

Baseline examination (Month 0) to determine cardiovascular risk factors

Body measurements

Weight, height

Waist and hip circumference (waist measured 5 cm above anterior superior iliac spine)

Familial medical history

Parents' medical history: Diabetes mellitus and obesity Premature cardiovascular disease in the family

Tobacco and alcohol

Tobacco use

Alcohol consumption

Vital signs

Blood pressure (in a sitting position, after 3-minute rest period)

Pulse (in a sitting position, after 3-minute rest period)

Laboratory parameters

Glucose after fasting (serum or plasma)

Lipid profile after fasting (HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides)

CRP

Documentation of cardiovascular events

Myocardial infarction

Stroke

Examinations over the course of the study (Month 3, 6, 12, 24, 36, 48, 60) to determine cardiovascular risk factors

Body measurements (except height)

Vital signs

Laboratory parameters

Tobacco use

Documentation of cardiovascular events

1.8 Calculation of CV risk model

In addition to the documentation tools described in AGIL:

SCORE (Systematic Coronary Risk Evaluation): The SCORE risk model is routinely used in European clinical practice to manage cardiovascular diseases. It permits a direct estimate of the absolute ten-year risk of fatal cardiovascular disease events. This ten-year risk calculation is based on the conditional probability of cardiovascular mortality within the next ten years, provided that the patient survives up to the index age (13).

The estimate is based on the absolute cardiovascular disease risk rather than just on the risk of coronary heart disease. The following parameters are used to calculate the score:

- Age
- Sex
- Currently smoker/non-smoker
- Systolic/diastolic blood pressure (in a sitting position, after 3-minute rest period)
- Cholesterol ratio (total cholesterol/HDL cholesterol)

The overall risk of fatal cardiovascular disease is calculated by combining two different risk estimates:

- Coronary heart disease
- Non-coronary atherosclerotic vascular disease

This calculation determines a probability score of fatal cardiovascular disease within the next ten years ranging from "< 1%" to "15% and over".

Risk models are to be modified for RA patients by applying a multiplication factor of 1.5 if a patient meets at least two of the following three criteria (1):

- Disease duration of over ten years
- Positive RF or positive anti-CCP antibody result
- Presence of certain extra-articular manifestations

1.9 Sample size estimation

Sample size estimation for AGIL-CV as a supplement to AGIL:

The sample size estimation is based on published data concerning the blood pressure of RA patients (14):

Assuming an alpha and beta error of 5% each, the following minimum number of RA patients is required at the evaluation time points of Months 12, 24 and 60:

- N=128 patients are required in order to detect a mean systolic blood pressure difference of 10 mmHg (given a mean systolic blood pressure of 128 mmHg with a standard deviation of 18 mmHg).
- N=136 patients are required in order to detect a mean diastolic blood pressure difference of 5 mmHg (given a mean diastolic blood pressure of 74 mmHg with a standard deviation of 11 mmHg).

In documentations with adalimumab, premature discontinuation has been observed for approx. 50% of patients in the course of a 60-month documentation duration. If this rate is taken into account; an overall number of N=300 patients is sufficient to address the primary research questions given the above-named estimations.

1.10 Biometrics concept of AGIL-CV

Biometrics concept as an addition to AGIL-CV:

Using stepwise regression analyses with forward and backward techniques, all partial correlations between the primary parameters and the other disease and patient characteristics are determined at baseline. The impact of disease and patient characteristics on the changes in each of the primary parameters is established by means of these regression analyses at Months 12, 24 and 60. In particular, the DAS28 response (defined as the critical difference [dcrit] of ≤ -1.8 points, constituting an improvement of 1.8 points in DAS28) or DAS28 nonresponse was used as a coded variable.

In addition, the observed difference between the DAS28 responders (patients with a dcrit of ≤ -1.8 at 5 of 7 visits) and the DAS28 nonresponders (dcrit > -1.8) is tested using the general linear model. Missing data are replaced using the Last observation carried forward (LOCF) method.

1.11 Time points of statistical analysis

Analysis time point of AGIL-CV as a supplement to AGIL:

Statistical analyses for the primary research questions are planned for Months 12, 24 and 60. For the secondary research questions, previous cardiovascular results are taken into account at these analysis time points.

1.12 References

The following references are to be added to the list:

(1) Peters, M.J.L., Symmons, D.P.M, Mcarey, D., et al. (2010). EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis; 69(2), 325-331.

(2) Del Rincon, I.D., Williams, K., Stern, M.P., et al. (2001). High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum; 44(12), 2737-2745.

(3) Han, C., Robinson, D.W.J., Hackett, M.V., et al. (2006). Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J Rheumatol; 63(11), 2167-2172.

(4) Ross, R. (1999). Atherosclerosis-an inflammatory disease. N Engl J Med; 340(2), 115-126.

(5) Maradit-Kremers, H., Nicola, P.J., Crowson, C.S., et al. (2005). Cardiovascular death in rheumatoid arthritis: a popular-based study. Arthritis Rheum; 52(3), 722-732.

(6) Dixon, W.G., Watson, K.D., Lunt, M., et al (2007). Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor-alpha therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum; 56(9), 2905-2912.

(7) Park, Y.B., Lee, S.K., Lee, W.K., (1999). Lipid profiles in untreated patients with rheumatoid arthritis. J Rheumatol; 26(8), 1701-1704.

(8) Vis, M., Nurmohamed, M. T., Wolbink, G., et al (2005). Short term effects of infliximab on the lipid profile in patients with rheumatoid arthritis. J Rheumatol; 32(2), 252-255.

(9) Van Halm, V.P., Peters M.J., Voskuyl, A.E., et al. (2009). Rheumatoid arthritis versus type 2 diabetes as a risk factor for cardiovascular disease: a cross- sectional study. Ann Rheum Dis; 68(9), 1395-1400.

(10) Popa, C., Netea, M.G., Radstake, T. et al. (2005). Influence of anti-tumor necrosis factor therapy on cardiovascular risk factors in patients with active rheumatoid arthritis. Ann Rheum Dis; 64(2), 303-305.

(11) Jacobsson, L.T., Turesson, C., Gulfe, A., et al. (2005). Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol; 32(7), 1213- 1218.

(12) Naranjo, A., Sokka, T., Descalzo, M.A., et al. (2008). Cardiovascular disease in patients with rheumatoid arthritis. Results from the QUEST-RA study. Arth Res Ther; 10(2), R30.

(13) Conroy, R.M., Pyorala, K., Fitzgerald, A.P, et al. (2003). Estimation of ten-year risk of fatal cardiovascular disease in Europe. The SCORE project. EIR Heart J; 24(11), 987-2003.

(14) Mok CC, Ko GT, Ho LY, et al. (2011). Prevalence of atherosclerotic risk factors and the metabolic syndrome in patients with chronic inflammatory arthritis. Arthritis Care Res (Hoboken). Feb;63(2):195-202.