Slik er planene for gjennomføring av byttestudien for biotilsvarende legemidler

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## Tore K Kvien – disclosures

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<tr>
<th></th>
<th>Honorarium</th>
<th>Institutional support NOR-DMARD</th>
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Editor-in-Chief Annals of the Rheumatic Diseases
A great interest of biosimilar mAbs in rheumatology

OPINION

The advent of biosimilar therapies in rheumatology—“O Brave New World”

Morton A. Scheinberg and Jonathan Kay

The role of biosimilars in the treatment of rheumatic diseases

Thomas Dörner,1,2 Vibeke Strand,3 Gilberto Castañeda-Hernández,4 Gianfranco Ferraccioli,5 John D Isaacs,6,7 Tore K Kvien,8 Emilio Martin-Mola,9 Thomas Mittendorf,10 Josef S Smolen,11 Gerd R Burmester1

Biosimilars in rheumatology: the wind of change

Christian K Schneider
EXTENDED REPORT

Inequities in access to biologic and synthetic DMARDs across 46 European countries

Polina Putrik,1 Sofia Ramiro,2 Tore K Kvien,3 Tuulikki Sokka,4 Milena Pavlova,5
Till Uhlig,6 Annelies Boonen,7 Working Group ‘Equity in access to treatment of
rheumatoid arthritis in Europe’

Figure 3  Access to biologic disease modifying antirheumatic drugs and gross domestic product per capita, international dollars (n=44). Size of the bubbles is proportional to the population size of the country. AL, Albania; AM, Armenia; AT, Austria; BA, Bosnia and Herzegovina; BE, Belgium; BG, Bulgaria; BY, Belarus; CH, Switzerland; CY, Cyprus; CZ, Czech Republic; DE, Germany; DK, Denmark; EE, Estonia; ES, Spain; FI, Finland; FR, France; GE, Georgia; GR, Greece; HR, Croatia; HU, Hungary; IE, Ireland; IS, Iceland; IT, Italy; KZ, Kazakhstan; LT, Lithuania; LU, Luxembourg; LV, Latvia; MD, Moldova; ME, Montenegro; MK, Macedonia; MT, Malta; NL, Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; RS, Serbia; RU, Russia; SE, Sweden; SK, Slovakia; SL, Slovenia; TR, Turkey; UA, Ukraine; UK, United Kingdom.
EXTENDED REPORT

Variations in criteria regulating treatment with reimbursed biologic DMARDs across European countries. Are differences related to country’s wealth?

Polina Putrik,1 Sofia Ramiro,2,3 Tore K Kvien,4 Tuulikki Sokka,5 Till Uhlig,6 Annelies Boonen,7 on behalf of Equity in Clinical Eligibility Criteria for RA treatment Working Group

Figure 1  Composite score for restrictiveness of clinical criteria for initiation of a first reimbursed biologic (0-5) in the European Region (score is composed of (1) minimum required disease duration, (2) number of sDMARDs that have to be failed and (3) the level of DAS28). DAS28, disease activity score with 28-joint assessment; sDMARDs, synthetic disease-modifying antirheumatic drugs.

AL, Albania; AT, Austria; BE, Belgium; BG, Bulgaria; HR, Croatia; CY, Cyprus; CZ, Czech Republic; EE, Estonia; FI, Finland; FR, France; DE, Germany; DK, Denmark; GR, Greece; HU, Hungary; IS, Iceland; IE, Ireland; IT, Italy; LV, Latvia; LT, Lithuania; LU, Luxembourg; MK, Macedonia; MT, Malta; ME, Montenegro; NL, the Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; RS, Serbia; SK, Slovakia; SI, Slovenia; ES, Spain; SE, Sweden; CH, Switzerland; TR, Turkey; UK, United Kingdom.
Figure 2  Composite score for restrictiveness of clinical criteria (0–5) and GDP per capita (int.$), n=36. Size of the bubble is proportional to the population size of each country. Dashed trend line is added to show the linear trend if without data from Luxembourg, which can be considered an outlier GDP, gross domestic product.

AL, Albania; AT, Austria; BE, Belgium; BG, Bulgaria; HR, Croatia; CY, Cyprus; CZ, Czech Republic; EE, Estonia; FI, Finland; FR, France; DE, Germany; DK, Denmark; GR, Greece; HU, Hungary; IS, Iceland; IE, Ireland; IT, Italy; LV, Latvia; LT, Lithuania; LU, Luxembourg; MK, Macedonia; MT, Malta; ME, Montenegro; NL, the Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; RS, Serbia; SK, Slovakia; SI, Slovenia; ES, Spain; SE, Sweden; CH, Switzerland; TR, Turkey; UK, United Kingdom.
EXTENDED REPORT

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study

Dae Hyun Yoo,1 Pawel Hrycaj,2 Pedro Miranda,3 Edgar Raminterre,4 Mariusz Piotrowski,5 Sergii Shevchuk,6 Volodymyr Kovalenko,7 Nenad Prodanovic,8 Mauricio Abello-Banfi,9 Sergio Gutierrez-Ureña,10 Luis Morales-Olazabal,11 Michael Tee,12 Renato Jimenez,13 Omid Zamani,14 Sang Joon Lee,15 Ho Ung Kim,16 Won Park,17 Ulf Müller-Ladner18

EXTENDED REPORT

A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study

Won Park,1 Pawel Hrycaj,2 Slawomir Jeka,3 Volodymyr Kovalenko,4 Grygorii Lysenko,5 Pedro Miranda,6 Helena Mikazane,7 Sergio Gutierrez-Ureña,8 Mi Jin Lim,1 Yeon-Ah Lee,9 Sang Joon Lee,10 Ho Ung Kim,11 Dae Hyun Yoo,12 Jürgen Braun13
Key question in Norway (and other parts of the world)

Can patients on treatment with Remicade be switched/transitioned to CT-P13 (Remsima or Inflectra) to reduce medication cost (and improve access to bDMARDs for more patients in areas with major financial restrictions)?

Is switching from innovator to biosimilar infliximab safe? (efficacy, safety, immunogenicity)

Limited switch data after 52 weeks are available in the PLANETRA and PLANETAS studies
Statsbudsjettet 2014:
Det foreslås 20 mill. kroner til kliniske studier

Det foreslås 20 mill. kroner til kliniske studier av bytte mellom biologiske og biotilsvarende legemidler.

Når et biologisk legemiddel går av patent åpnes det for at andre produsenter kan lage tilvarende biologiske legemidler.

Det er som oftest ikke mulig å lage helt identiske kopier av biologiske legemidler slik tilfellet er med syntetiske legemidler (generika), herav navnet biotilsvarende.

Når europeiske legemiddelmyndigheter godkjenner et biotilsvarende legemiddel, er det en bekreftelse på at det har samme virkning som originallegemidlet.

Ev. bytte mellom det originale biologiske legemidlet og det biotilsvarende legemidlet hos pasienter som allerede får behandling, er ikke en del av godkjenningen.
Formålet med studiene er å dokumentere hvorvidt slikt bytte er trygt.

Satsingen er i tråd med forslag om å styrke offentlig initierte kliniske studier innenfor andre fagområder enn kreftområdet, hvor det i dag pågår en satsing gjennom Norges forskningsråd.


Denne type forskning vil normalt ikke bli finansiert av kommersielle aktører og ofte heller ikke alltid være attraktiv for forskergrupper å initiere, men vil kunne gi resultater med stor samfunnmessig verdi.
A RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP STUDY TO EVALUATE THE SAFETY AND EFFICACY OF SWITCHING FROM INNOVATOR INFLIXIMAB TO BIOSIMILAR INFLIXIMAB COMPARED WITH CONTINUED TREATMENT WITH INNOVATOR INFLIXIMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS, SPONDYLOARTHRITIS, PSORIATIC ARTHRITIS, ULCERATIVE COLITIS, CROHN’S DISEASE AND CHRONIC PLAQUE PSORIASIS THE NOR-SWITCH STUDY
Feasibility

• The study has to be feasible – should be part of daily clinical practice. Therefore, design and data collection must not be too complicated or comprehensive.

• However, the study should be performed with a high quality – from both the scientific and regulatory perspective.
Objectives

Primary:
• To assess if CT-P13 is non-inferior to innovator infliximab (INX) with regard to disease worsening in patients who have been on stable INX treatment for at least 6 months

Secondary:
• To assess the safety and immunogenicity of CT-P13 compared to INX on patients who have been on stable INX treatment for at least 6 months
• To compare the efficacy of CT-P13 to INX in patients who have been on stable INX treatment for at least 6 months applying generic and disease-specific outcome measures

Exploratory:
• To compare cost-effectiveness of CT-P13 to INX in patients who have been on stable INX treatment for at least 6 months
Patient population

• Patients
  – RA, SpA inkl PsA
  – IBD
  – Psoriasis
• Adults on stable treatment with Remicade for at least 6 mnd
• Ethics
  – Will patients on successful treatment be willing to be randomized?
  – What will be the alternative treatment for patients who decline to participate (continue Remicade or switch to Remsima to reduce costs – assuming that the drugs are similar)
Inclusion criteria

• A clinical diagnosis of either rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn’s disease or psoriasis
• Male or non-pregnant, non-nursing female
• >18 years of age at screening
• Stable treatment of innovator infliximab (Remicade) during the last 6 months
• Subject capable of understanding and signing an informed consent form
• Provision of written informed consent
Exclusions

• Major co-morbidities, such as severe malignancies, severe diabetic mellitus, severe infections, uncontrollable hypertension, severe cardiovascular disease (NYHA class 3 or 4) and/or severe respiratory diseases

• Change of major co-medication during the last 2 months:
  – RA, SpA and PsA: Initiation of systemic corticosteroids or synthetic DMARDs or other medication which according to the investigator would interfere with the stability of the disease.
  – UC and CD: Initiation of systemic corticosteroids or an immunosuppressant or other medication which according to the investigator would interfere with the stability of the disease
  – Psoriasis: Initiation of synthetic DMARDs or other medication which according to the investigator would interfere with the stability of the disease

• Inadequate birth control, pregnancy, and/or breastfeeding

• Psychiatric or mental disorders, alcohol abuse or other substance abuse, language barriers or other factors which makes adherence to the study protocol impossible

• Change in treatment with innovator infliximab (Remicade) during the last 6 months due to disease related factors
Medication- dosage and drug administration

• Biosimilar infliximab (Remsima or Inflectra): CT-P13

• The dose of both drugs (Remicade or CT-P13) will be identical to the dose of innovator infliximab (Remicade) before randomization. Both drugs will be administered as intravenous infusions.
Schedule Modifications

• The main rule is that treatment will continue on the same dose and the same infusion intervals during the 52-week follow-up period. However, changes in dose and interval may be permitted due to non-disease related factors such as intercurrent infections, surgery, vacation, etc. at the discretion of the treating physician.

• Drug levels will be measured at each assessment, but only reported on request. Changes in dose/interval based on drugs levels is not part of the treatment regimen.
Design

• RCT – 1:1 – (stratification according to disease, co-medication, other factors)
• Blinding procedures
• Primary endpoint
  – Occurrence of disease worsening during the 52-week study period based on disease specific efficacy assessment scores
• Several secondary study endpoints
• Follow-up 12 months
• Biobank
Endpoints

Primary endpoint:
Occurrence of disease worsening during the 52-week study period based on disease specific efficacy assessment scores

Secondary endpoints:
Generic:
• Time from randomization to disease worsening
• Patient and Physician Global assessment of disease activity
• Occurrence of drug discontinuation
• Time from randomization to drug discontinuation

Disease-specific:
• Inflammation assessed by biochemical parameters
• RA and PsA: DAS28, M-HAQ, RAID, PsAID
• SpA: ASDAS, MHAQ, BASDAI
• Psoriasis: PASI, DLQI
• UC: Partial Mayo score, IBDQ
• CD: HBI, IBDQ

Exploratory endpoints:
• EQ-5D
• SF-36
• WPAI-GH
• Use of health care resources
Disease worsening

**Disease worsening in RA and PsA**
A disease worsening in RA and PsA is defined as an increase in DAS of ≥1.2 from randomization, a minimum DAS score of 1.6

**Disease worsening in SpA**
A disease worsening in AS/SpA is defined as an increase in ASDAS of ≥1.1 from randomization

**Disease worsening in ulcerative colitis**
A disease worsening in ulcerative colitis is defined as an increase in partial Mayo score of ≥ 3 points from randomization and a minimum partial Mayo score of ≥ 5 points.

**Disease worsening in Crohn’s disease**
A disease worsening in Crohn’s disease is defined as an increase in HBI of ≥ 4 points from randomization and a minimum HBI score of 7 points.

**Disease worsening in psoriasis**
A disease worsening in psoriasis is defined as an increase in PASI of ≥ 3 points from randomization and a minimum PASI score of 5.

**Patient and investigator consensus on disease worsening**
If a patient does not fulfill any of the formal definitions above, experienced clinically significant worsening according to both the investigator and patient will be considered as fulfillment of the primary endpoint, but recorded separately in the CRF.
6. 2. Discontinuation

- **Criteria for Patient Discontinuation**

  Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient for this study are:
  - Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment.
  - Safety reason as judged by the Principal Investigator
  - Major protocol deviation
  - Incorrect enrolment ie, the patient does not meet the required inclusion/exclusion criteria for the study
  - Patient lost to follow-up
  - A female patient becoming pregnant
  - Major disease progression
  - Deterioration in the patients condition which in the opinion of the Principal Investigator warrants study medication discontinuation (to be records as an AE or under Investigator Discretion)
  - Patient’s non-compliance to study treatment and/or procedures
Statistics/power

- Non-inferiority
- Primary endpoint estimated to occur in 30% during 52 weeks
- Equivalence criteria ± 15%
- Power 90%
- 500 patients to be randomized (20% withdrawals)
Table 1: The numbers in the cells represent the total number of patients needed in total. All calculations are based on a power of 80% and alpha 2.5%.

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<td>504</td>
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<td>15%</td>
<td>126</td>
<td>224</td>
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<td>20%</td>
<td>72</td>
<td>126</td>
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Table 2: The numbers in the cells represent the total number of patients needed in total. All calculations are based on a power of 90% and alpha 2.5%.

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<tr>
<td>10%</td>
<td>380</td>
<td>674</td>
<td>884</td>
</tr>
<tr>
<td>15%</td>
<td>170</td>
<td>300</td>
<td>394</td>
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<tr>
<td>20%</td>
<td>96</td>
<td>170</td>
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Organisation

- **Coordinating center:** Dept of Rheumatology, Diakonhjemmet Hospital (on behalf of the South-East Health region authority)
- **Multidisciplinary and multiregional project group** with special competence in statistics (power calculations), immunogenicity, health economic evaluations, performance of strategy trials.
- Representation from NorCRIN
- Representation from the three relevant patient organisations
- Working group with a dermatologist, gastroenterologist, rheumatologist, statistician and expert in strategy studies (TKK, leader)
- The project will have a dedicated project coordinator and also three young fellows supporting the project (and being involved in publishing the results).
- Electronic CRF
- Monitoring of the study will most likely be performed by the regional health authorities
Conclusions

• Access for patients to biological disease-modifying antirheumatic drugs (bDMARDs) is strongly correlated to the economy in different countries. It can be expected that lower price of bDMARDs will improve accessibility and lead to better treatment.

• The availability of biosimilar infliximab (Remsima/Inflectra) is a new opportunity for lowering the cost of treatment with bDMARDs.

• Biosimilar infliximab (Remsima and Inflectra) was approved by the European Medicines Agency (EMA) and the Norwegian health authorities in the fall 2013.

• In the Norwegian tender system Orion Pharma offered a discount of 39% compared to the price of Remicade whereas Hospira offered a discount of 33%. Thus, Remsima is the preferred infliximab in 2014 based on this price system.

• Safety, efficacy and immunogenicity related to switching from Remicade to CT-P13 (Remsima/Inflectra) will be explored in a govermental supported study in Norway – designed as a non-inferiority RCT.