BIOSAFE trial : Efficiency of a Nurse-led self-management education intervention in promoting safety knowledge and skills of patients with arthritis treated par biologics

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Catherine Beauvais is Rheumatologist. Her field of expertise is patient education, particularly for patients with inflammatory arthritis [1- 6]. In Saint Antoine Hospital she is in charge of 2 Self-management education programs for patients with inflammatory arthritis and osteoporosis. She is president of the Therapeutic education section of The Société Française de Rheumatologie (SFR) since 2008. She is in charge of a Patient education training course In PARIS VI University for health professionals and MDs, and is now launching a rheumatology nurse training course. She has been investigator in clinical trials in the field of RA [7] and education. She has built a long standing collaboration with patients' organization.

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Project Summary

Efficiency of a nurse-led self-management education intervention in promoting safety knowledge and skills of patients with arthritis treated par biologics : the BIOSAFE trial.

Abstract (400 words)

Inflammatory arthritis (rheumatoid arthritis (RA) or spondyloarthritis (SpA) affect approximately 600.000 patients in France. They are painful chronic diseases which impair quality of life and work capacity. Biologics are very effective and widely used therapies. However, they are known to entail risks, particularly of infections. The risk of severe infections is of 5%/patient-year with a maximum during the first six month after the initiation of the first biologic treatment [8].
Patient education (PE) aims to help patients to learn specific skills particularly on safety issues [2]. PE is recommended by the National health authorities for the management of chronic diseases [9]. Safety skills are assessed by the validated Biosecure questionnaire [2] , a 54 item questionnaire assessing patients competences to deal with fever, infections, vaccination, and other daily life.
PE seems efficient for safety skills in a few non-randomized studies [10,11]. In 2010 a national cross sectional survey on 677 patients showed that the risk of incorrect answers in the Biosecure questionnaire was 4 times lower among patients who had benefited from an education by a nurse or other kind of educational process [4].
This simple-blinded multicentric randomized controlled trial aims to investigate the effects of a nurse-led self-management education face to face intervention on safety Knowledge and skills of patients with arthritis treated par sub cutaneous biologics. Our hypothesis is that the intervention group will report better skills at the 6 months follow up compared to usual care i.e information by the rheumatologist in current consultation.
120 patients with RA, SpA and Psoriatic arthritis (PsoA) will be enrolled in 10 rheumatology centers during a 12 months inclusion period. The intervention group will have a nurse education consultation at M 0 and M3. The nurse will assess the patients' health beliefs and educational needs, will focus education on safety skills, self-injections and motivation. All patients will be assessed at M0 and M6. At M6, the primary outcome will be the score of the

Biosecure Questionnaire. The secondary outcomes will be adherence to the biologic treatment, quality of life, coping, severe infections rate, and disease activity.
This trial is the first RCT in the field of patients education on safety issues. In case of positive results, the impact will be a potential decrease of adverse effects and an improvement of adherence to biologics at 6 months as well the development of nurse-led self-management programs for patients with arthritis.

Lay Case for Support (french)

Etude BIOSAFE : Efficacité de l'éducation thérapeutique réalisée par une infirmière sur l'acquisition par les patients souffrant de rhumatisme inflammatoire chronique de compétences de sécurité vis-à-vis des les biothérapies.

Contexte
Les rhumatismes inflammatoires chroniques (RIC) (la polyarthrite rhumatoïde (PR) et les spondyloarthroarthrites (SpA) sont des affections invalidantes touchant 600 000 patients en France. Les RIC entraînent un handicap, et une exclusion prématurée du monde du travail. Le traitement des RIC a été transformé par les Biothérapies qui, cependant ne sont pas dénués de risques, en particulier d'infections graves. Pour chaque patient, le risque d'infection grave est évalué statistiquement à 5% par année de traitement, avec un maximum dans les 6 premiers mois suivant la prescription de la première biothérapie. En France des programmes d'éducation thérapeutique, le plus souvent réalisés par des infirmières, aident les patients à gérer les risques, leur permettant de vivre avec la biothérapie en profitant des bénéfices du traitement sur leur santé. Ces consultations infirmières semblent efficaces et appréciées des patients mais n'ont pas encore été évaluées scientifiquement. Par exemple, lors d'une grande enquête nationale réalisée en 2010 sur 677 patients, les patients qui avaient eu une éducation avec une infirmière ou dans un programme, semblaient 4 fois plus capables de répondre correctement à un questionnaire d'évaluation des compétences de sécurité, le questionnaire Biosecure. Ainsi ils semblaient mieux connaitre la gestion des risques infectieux (par exemple arrêt de la
biothérapie en cas de fièvre), les mesures à prendre en cas de voyage, chirurgie, désir de grossesse, vaccinations etc.

Questions posées
Cette étude tentera de répondre à la principale question suivante : 2 consultations infirmière réalisées lors de l'initiation d'une biothérapie SC et 3 mois plus tard apportent-elles vraiment un bénéfice sur la sécurité des patients ?
Cette étude tentera également de répondre à d'autres questions : on sait déjà que lors de l'initiation d'une biothérapie SC, il est important que les patients se sentent accompagnés car il existe alors une meilleure adhésion, c'est-à-dire que les patients prennent mieux leur traitement. Cette étude permettra de savoir si les consultations augmentent cette adhésion avec une meilleure chance d'atteindre l'objectif de rémission ou de faible activité du rhumatisme.

Réalisation de l'étude
120 patients participeront à cette étude, dont la moitié soit 60 patients bénéficieront des consultations infirmière dès l'introduction de la biothérapie et au bout de 3 mois. L'autre

moitié soit 60 patients bénéficieront d'une consultation infirmière seulement à la fin de l'étude c'est à dire au bout de 6 mois. Les compétences de tous les patients seront évaluées à 6 mois et l'analyse statistique recherchera si les patients éduqués par l'infirmière ont de meilleurs résultats au questionnaire Biosecure. L'analyse recherchera également si les patients éduquées prennent mieux leur traitement, ont moins d'infections, et font mieux face à la maladie.
Cette étude est la première étude scientifique sur l'acquisition par les patients traités par biothérapie de compétences de sécurité. Si elle montre que les consultations infirmières apportent un bénéfice, particulièrement pour la sécurité, il sera alors important que les patients puissent y avoir accès. Les résultats de cette étude auront donc des implications sur l'organisation des soins pour un meilleur accès des patients à l'éducation thérapeutique. En effet et comme l'avait montré l'enquête de 2010, bien que l'éducation thérapeutique soit entrée dans le parcours de soins du patient par la loi HPST de 2009, tous les patients sous biothérapie n'y ont pas accès.

Expertise and Facilities (1200 words each section)

Expertise

The Saint Antoine rheumatology department and the 10 rheumatology centers participating the trial have a recognized expertise in clinical trials and research. They all have expertise and experience in patients' education in the management of inflammatory arthritis [3,4,10]
Pr Simon is the Director of the Clinical Research platform of the East of Paris, including the Clinical Research Center (CRC-EST), and the Certified BioBank Research Center (CRB) of UPMC-Paris 06 University and University Hospital group of East of Paris and the Clinical Research Unit (URCEST:http://www.urcest.chusa.upmc.fr/)

This trial is developed by 2 clinical teams (C. Beauvais and L. Gossec) who have been working on patient education related to safety issues of biologics. They have elaborated and validated the Biosecure questionnaire assessing patients' self-care safety skills. This work was performed due to the collaboration between rheumatologists, patients and allied health professionals, including 4 co applicants [2]. The biosecure questionnaire has been used for A national cross-sectional by AC Rat (coapplicant) in 2010 [4]. This survey was supported by a patient'organization. Sophie Pouplin (co applicant) has also conducted a open trial on group Intervention on self-management of biologics [10].

The present trial is therefore the result of previous work, by several clinical teams which have experience and expertise in management of biologics treatment and patient education.
The co applicant of the 10 rheumatology centers are members of the French Rheumatology Society Therapeutic Education section. This section includes rheumatologist and allied health professionals. The role of the section is promoting research of patient education and self-management programs. The Section has also developed a training course for patient education in the field of rheumatic diseases (PARIS VI). All the investigating nurses have received a training on patient Education. (8/10 nurses have the degree of the of the PARIS

VI education course) . The investigating nurses of 8/10 centers have a direct experience of clinical trial in nurse-led programs. The other 2 centers include nurses who also have an experience the self-management program assessment . All nurses belong to a multidisciplinary team for patient education.

Facilities

This multicentric trial will be conducted in 10 secondary and tertiary- care rheumatology centers. The patients will be recruited out of the cohort of patients currently referred to the centers for initiation of biologic treatment. The recruitment of eligible patients will be done in consultation according to the inclusion criteria.
The intervention will be performed by 1 or 2 nurses, depending of the centers' organization of care. The intervention will be standardized among nurses.
In each center, the rheumatologists in charge of the initiation of biologic treatment will request the patient participation to the trial, will do the medical consultation, usual care information and baseline assessment.

The Clinical Research Unit of GH HUEP – Pr Tabassome SIMON will be in charge of the methodology, regulatory aspects and logistic coordination, data management and statistical analysis.

Each center will include 12 patients during a 12 months inclusion period, which represent a small number of patients compared to the patients with inflammatory arthritis currently followed up in these centers.
Qualified human resources for inclusion, follow up and data management are therefore available and the feasibility of the trial is high.

Aims and Objectives
This simple-blinded multicentric randomized controlled trial (RCT) is designed to investigate the effects of a nurse-led self-management face to face education intervention on safety knowledge and skills of patients with arthritis treated par biologics. Our hypothesis is that the intervention group will report better skills at the 6 months follow up compared to the control group with usual care.

Proposal (3000 words)

Background and objective
Inflammatory arthritis (rheumatoid arthritis (RA) or spondyloarthritis (Sondylitis and psoriatic arthritis) affect approximately 600.000 patients in France. They are painful chronic diseases which impair quality of life and work capacity. Biologics are very effective and widely used therapies. However, they are known to entail risks, particularly of infections such as pulmonary infections, tuberculosis, and a few cases of opportunist infections. The risk of severe infections is of 5%/patient-year with a maximum during the first six month after the initiation of the first biologic treatment [8].

Patient education (PE) aims to help patients to learn specific skills particularly on safety issues. PE is recommended by the National health authorities for the management of chronic diseases [9]. Safety skills are assessed by the validated questionnaire Biosecure, a 54 item questionnaire assessing patients competences to deal with fever, infections, vaccination, and other daily life situations ie travelling, surgery, pregnancy [2].
PE seems efficient for safety skills in a few non ramdomized studies [10,11]. In 2010 a French [4] national cross sectional survey showed that the risk of incorrect answers in the Biosecure questionnaire was 4 times lower among patients who had benefited from an education by a nurse or other kind of educational process. Although PE is recommended, a small rate of patients had been proposed PE : 30% patients had had a face to face nurse consultation and for 11% patients the nurse consultation was part of a self-management program.
This single blinded multicentric randomized controlled trial (RCT) is designed to investigate the effects of a nurse-led self-management face to face intervention on safety Knowledge and skills of patients with arthritis treated par biologics. Our hypothesis is that the intervention group will report better skills at the 6 months follow up compared to the control group.
When a biotherapy is initiated, the initiation period is known to be critical for the patients motivation and adherence, particularly for patients treated by sub cutaneous biotherapy [12]. This trial will include adherence in the secondary outcome. Our hypothesis is that the nurse intervention will increase motivation and adherence.

Participants
120 in and out patients with RA, SpA and Psoriatic arthritis (PsoA) will be enrolled in 10 rheumatology secondary or tertiary centers during a 12 months inclusion period.

Inclusion criteria :
Age 18-75 years
Patients with RA (ACR/EULAR criteria), axial or peripheral Spondyloarthritis (ASAS criteria), Psoriatic Arthritis (CASPAR criteria), patients who are eligible for a Sub cutaneous biologic treatment according to the French recommendations of care, patients naïve from biologics.
Patients benefiting from French Social Security insurance.

Exclusion criteria
Patients unable to speak or read French language,
Patients unable to complete a questionnaire or meet with the trial obligations
Patients suffering from severe cognitive or psychiatric dysfunction
Patients who will not have signed the informed consent

Intervention (see flow chart in annex 1).

The pre selection visit will take place during the medical consultation. The rheumatologist will check the eligibility, according to the inclusion/ exclusion criteria. Eligible patients will receive written information and will be invited to participate in the RCT.
During the selection visit at M0, all patients will receive current information by the hospital rheumatologist.

After signing the informed consent form, at M0 all patients will be assessed for baseline characteristics. The randomization schedule will be prepared by the biostatistician using a computer-generated random numbers. The randomization will take place after the medical consultation and completion of the baseline assessment, in order to preserve the blinding. After randomization, the participants will be either in the intervention group (IG) or the control group (CG). Patients of the intervention group will be referred to the nurse, the same day or within 1 week after inclusion.

Nurse intervention

At M0, the nurse face to face intervention will include 1/ assessment of the patients' health beliefs and educational needs towards arthritis and treatment through a semi directive questionnaire to enhance communication 2/ Information about biologics 3/ specific education on safety skills and self-injections 4/ Motivational communication on biologics treatment.

At M3, the nurse will communicate on the patient's experience and motivation and will reinforce the safety messages.

The MO intervention will last less than 1 hour 30 and the M3 less than 1 hour, the actual duration of the consultation will be left to the nurse's appreciation depending on the patient's needs.

The nurse intervention will be will be standardized among centers by 2 or 3 telephone conferences. A physical meeting is not considered necessary as most nurses already know each other through the SFR Section, previous training and previous meeting for the other trials. A dedicated booklet will summarize the components of the educational diagnosis : assessment of the patients of educational needs, safety messages and motivational messages. The elaboration of the booklet will derive from previous work on the Biosecure study [2] recommendations for PE [9] and previous work on educational needs of arthritis patients [5,13].

Baseline characteristics

Baseline assessment will include demographics features, age, gender, education level, disease duration, type of arthritis (RA versus SpA), disease activity measured by the DAS 28 (Disease Activity index) [14] for the patients with RA and the BASDAI (Bath ankylosing spondylitis disease activity index) [15] for the patients with SpA, previous knowledge about arthritis.

Follow-up

Patients of both groups (IG and CG) will be followed up by their rheumatologist in hospital or private care according to usual management of biologics treatment.

Final assessment

Patients of both groups (IG and CG) will be assessed at M6 for primary and secondary outcomes.
The administration of the questionnaires will be done by a member of the multidisciplinary team blinded for the treatment group.
An additional nurse consultation will be proposed independently to the trial to patients whose safety knowledge will be proved to be inadequate at M6 assessment.

Outcomes

Primary outcome criteria : Comparison of safety skills assessment by the Biosecure Questionnaire between the 2 groups at M6.

Primary criteria measure: score of the Biosecure Questionnaire [2].

Secondary outcomes criteria :
Comparison of the adherence to biologics between the 2 groups at M6
Comparison of the variation of Quality of life, Coping and Disease activity (DAS or BASDAI) between the 2 groups at M6
Comparison of the rate of severe infections between the 2 groups at M6
Correlations between the patients skills and Baseline characteristics

Secondary outcome measures
Adherence to the biologics : Modified Moritsky adherence scale) [16].
Quality of life : SF12 [17].
Coping : VAS derived from the RAID [18] score and AIH arthritis helplessness index [19].
Severe infections rate, defined as infections requiring Intravenous Anti biotherapy or hospitalization.

The primary outcome, adherence, and the rate of severe infections will only be collected at M6.
All other outcomes will be collected at M0 and M6. Satisfaction of the intervention will be assessed in the intervention group [19].

Correlations will be analyzed between the patients skills and age, gender, education level, disease duration and type of arthritis (RA versus SpA).

Sample size calculation

Considering a BioSecure score of 68.08±18.28 without PE and an expected relative increase of 15% of BioSecure Score with PE compared to the group without PE [4] with alpha =5%, beta=20% and 15% of patients lost of follow-up, 120 patients are needed.

Time schedule

The inclusion period will be of 12 months. Each patient will be followed during 6 months (+/- 1 month) after inclusion.

Ethics

The study will be conducted according to recommendations of good clinical practice. The protocol will be submitted to the Comité de Protection des Personnes (CPP) of Saint Antoine hospital. An authorization for collecting patients' data will be requested at the Commission Nationale de l'Informatique et des Libertés (CNIL). All patients with benefit from written information. An informed consent will be signed before entering the study.

Impact (400 words)

This trial is the first RCT in the field of patients self-management of biologics safety issues.
If the results are positive, the impact for patients will be 1/ a potential decrease of adverse effects, especially during the first 6 months which are the most critical regarding safety. 2/ a potential better adherence to biologics, whereas the initiation period is known to be critical for the patients motivation. A better adherence could subsequently benefit in a better disease control at 6 months.
If the results are positive, the impact for heath organizations will be 1/ demonstration of the role of nurses in self-management programs for inflammatory arthritis , especially on safety issues. 2/ Since biologics currently require a hospital prescription, there will be an impact on hospital organization to provide the safer care for the patients.
The standardized intervention and assessment by the Biosecure Questionnaire used in this trial will potentially be disseminated to other rheumatology centers and to private multidisciplinary centers.
The impact will also be important regarding research on patient education in the direction of health authorities and health regional agencies which give the authorizations for PE education programs in France

Public Engagement (400 words)

Recruitment will begin in January 2015. As the biologics require a hospital prescription, the source of recruitment will be the patients referred in the 10 rheumatology centers for initiation of the biologic treatment. Rheumatologist who address the patients will be informed of the protocol.

The results will be disseminated though national and international meetings in rheumatology (SFR, EULAR, ACR) and patient education (SETE Société européenne d'éducation thérapeutique) , national meeting of the SFR Therapeutic education section, Rencontres nationales des rhumatismes for patients and allied health professionals .
The results of the trial will be proposed for publication to international reviews.
The PA will communicate on ANDAR and France Rhumatismes support which will be mentioned on any presentation or publication on this trial.

Exploitation (800 words)

Statistical analysis principles.

Statistical analysis will be performed on the ITT population.

Baseline characteristics will be described in both groups.

Self-care safety skills will be assessed with BioSecure questionnaire score at baseline and at 6 months. Difference (M6-M0) will be compared between the two groups using Student t Test or non-parametric test when appropriate.

Secondary evaluation criteria will be compared using Pearson Chi square test or Fisher exact test for qualitative data and student t test or Wilcoxon non parametric test for quantitative data. Multidimensional scales will be analyzed according to their components scores.

Industrial Support

No industrial support will be requested.

Finance and Costs

Expenses	**Details**	**2015**	**2016**	**Total euros**
Salaries				
Coordination		2550	2550	5100
Clinical research technician		5812,50	5812,50	11625
Clinical research associate		3200	6400	9600
Data manager		3875	3875	7750
biostatistician		2450	7450	9800
Coordination Research Unit		4000		4000
Total Salaries				**47875**
Global Expenses				
Impression booklets				2750
Impression Questionnaires				1620
Impression CRF				4800
Randomisation		861,12		861,12
Travel expenses		1067	2133	3200
Postage expenses				400
Total				14158,12
Management fees 10%				6893

TOTAL				68 926,12

An additional grant will be requested to the French Rheumatology Society Therapeutic Education section.

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