Investigator iniciated trials in Portuguese rheumatology

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Randomized controlled clinical trials (RCTs) are considered the highest level of evidence in human experimental medicine. Usually designed to assess the efficacy and safety of new therapies or treatment strategies, that ultimate led to its approval and application in clinical practice; they are, in the majority of cases, funded and conducted by a pharmaceutical company. Investigator initiated trials (IIS) are often a unique way to answer particularly relevant questions to clinical practice. They complement available safety and efficacy information and sometimes the mechanism of action, of a specific therapy. While searching at clinicaltrials.gov, 835 IIS can be identified from a total of more than 200,000 registered studies, indicating that ISS are still a small fraction of the running clinical studies. IIS needs to be encouraged and supported in order to improve evidence-based decision-making and consequently bring maximum public health benefits.

The development of an IIS starts from a clinical research question. Indeed, physicians while providing medical care for patients often are confronted with relevant clinical questions: which treatment is the best option for this disease or symptom? Is there any marker of treatment response? Which symptom is predictor of a poor outcome? In order to test the clinical hypothesis, the adequate design (blinded/open, controlled/non controlled), treatment-arms, length of therapy, permitted concomitant therapy have to be defined at an early phase of protocol development. The outcome measures for accessing the primary (and secondary) endpoint have to be carefully chosen to ensure validity of results. Finally, regulatory aspects must be taken into account, and approvals of the National regulatory authorities that guarantee the protection and confidentiality of patients data (Comissão Nacional de Protecção de Dados), ethic issues (Comissão Ética para a Investigação Clínica) and the experimental drug (INFARMED) should be required for the trials including IIS. Clinical trials testing medical devices follow the same rules as medications, with some particularities depending upon the type of trial and device's specificities[1].

To conduct IIS, cooperation among several stakeholders[2] is necessary, which represents an organizational effort for clinical investigators, hospitals, academia, research sponsors, patients, physicians, and regulator. Each stakeholder offers a different set of tools to support the essential components of a clinical trial. In fact, Clinical Investigation Centres based at Hospitals, can be of help to the investigators to develop and implement clinical trials. Furthermore, academic institutions either Universities or research Institutes have facilities such as biostatistics, legal support and communication offices. Pharmaceutical industry is a fundamental partner for the success of an IIS, through the promotion of research grants and a know-how for conducting RCTs. Together, these stakeholders create the infrastructure that supports clinical research.

The Portuguese Rheumatology Society (SPR) has recently supported 3 IIS in distinct areas: the GO-DACT, the biomarkers in AS and ViscoOA.

GO-DACT is a nationwide multicentre, interventional, double-blinded, placebo-controlled, parallel design trial of golimumab in combination with MTX versus MTX monotherapy, in MTX-naïve psoriatic arthritis patients with active dactylitis. This trail aims to demonstrate differences of efficacy of golimumab in combination with MTX in comparison with MTX monotherapy, in improving dactylitis at 24 weeks versus baseline, in MTX-naïve PsA patients. GO-DACT Includes patients older than 18 years, with the diagnosis of psoriatic arthritis according to the CASPAR criteria[3], and ≥1 tender dactylitis, refractory to at least two systemic NSAIDs, at optimal dosage, for 3 months. Each subject will participate in the trial for a maximum of approximately 32 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of approximately 28

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days, each subject will receive the assigned treatment for 6 months. Study visits are performed at baseline, week 4, week 12 and week 24. After the end of treatment, each subject will be followed for safety monitoring and sustained efficacy assessment for 60 days. Data to assess disease activity (dactylitis, enthesitis, psoriasis, nail, peripheral and axial disease), functionality, health status (SF-36), quality of life (QoL), Dermatology Life Quality Index (DLQI) and adverse events are collected; peripheral blood samples are also collected. Magnetic resonance imaging (MRI) of the wrists and hands or the feet and ankle are performed according to a pre-determined protocol at baseline and week 24 depending on dactylitis location. If both, hand and feet fingers, are involved the most severely affected area, will be selected. GO-DACT primary endpoint is changes from baseline of the Dactylitis Severity Score (DSS) at 24 weeks. Secondary efficacy endpoints include: (1) Changes from baseline of dactylitis MRI score at week 24; (2) Changes from baseline of the LEI and SPARCC scores at 12 and 24 weeks; (3) Changes from baseline in 68 tender and 66 swollen joint counts at 12 and 24 weeks; (4) Changes from baseline of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis (AS) Disease Activity Score (ASDAS) at 12 and 24 weeks, in patients with axial involvement; (5) Proportion of patients achieving Psoriasis Area and Severity Index (PASI) 50, 75 and 90 response at 12 and 24 weeks; (6) Changes from baseline in target Nail Psoriasis Severity Index (target NAPSI) score, at week 12 and 24; (7) Changes from baseline in functional indexes Health Assessment Questionnaire Disability Index (HAQ) and Bath Ankylosing Spondylitis Functional Index (BASFI) at 12 and 24 weeks (for complete description of study design and endpoints see: Clinicaltrials.gov: NCT02065713).

"Biomarkers identification of anti-TNF α agent's efficacy in Ankylosing Spondylitis (AS) patients using a transcriptome analysis and mass spectrometry" is an ongoing prospective, single-arm, open-label, multicentre IIS, designed to identify new candidate genes and proteins that are differentially expressed in responders *vs* non-responders to anti-TNF therapy.

Patients with AS according to SPR guidelines (1984 modified New York Criteria, but allowing the use of MRI as imaging criteria for sacroiliitis)[4] from seven Portuguese Hospitals, in whom anti-TNF therapy is indicated according to the Portuguese recommendations for the use of biological therapies[4] are included and receive adalimumab every other week, during a follow-up period of 14 weeks. Study visits are performed at baseline, 3-5 days, week 2 and week 14. Data related with disease activity, functionality, metrology, quality of life (QoL), adverse events are collected as well peripheral blood samples. MRI of the entire rachis and SI joints is performed before baseline and after week 14, according to a predetermined protocol. At week 14 the whole group is divided in responders and non-responders according to ASAS 20 criteria. The signature profiles between these 2 groups will be analysed. The study main aim is to identify biomarkers (gene and/or proteins) predicting efficacy to anti-TNF therapy, as defined by the ASAS 20 response-criteria. Secondary aims include: (1) identification of biomarkers (gene and/or proteins) predicting efficacy to anti-TNF therapy according to the ASDAS response-criteria; (2) Bone and muscle MRI-changes under TNF therapy; and (3) QoL changes under TNF therapy. For additional information related with the study protocol see ClinicalTrials.gov: NCT02492217.

ViscOA is an ongoing randomized double-blind placebo-controlled IIS designed to test the hypothesis that Intra-Articular Hyaluronic Acid (IAHA) is superior to placebo in slowing structural progression and on long-term symptomatic effect in primary knee Osteoarthritis (KOA).

Patients with symptomatic KOA according to the American College of Rheumatology (ACR) clinical and radiographic criteria[5] from two Portuguese academic hospitals are included and randomized to receive either four 6-monthly injections of (high molecular-weight) IAHA or placebo (saline solution) during a total follow-up period of 24 months. Study visits are performed every 12 weeks in order to measure pain, function, quality of life, possible adverse events, pain-medication and for blood-samples collection. Radiographs, performed by trained technicians according to pre-determined protocol, are taken at baseline, one year and 6 months after the last injection (2-years). The study primary endpoint is the mean-change on the minimal joint space width of the most affected compartment of the tibiofemoral joint at the end of follow-up (2 years). Secondary efficacy endpoints include: (1) proportion of patients achieving symptomatic relief according to OMERACT/OARSI 2004 response criteria[6] at 6 months; (2) proportion of patients submitted to knee replacement surgery at the end of follow-up; and (3) use of pain-medication at each follow-up visit. In addition, the role of explo-

ratory outcomes, including ultrasonography measurements and serum biomarkers, in KOA-assessment will be tested (for complete description of study design and endpoints see: Clinicaltrials.gov: NCT02280538).

The Portuguese Society of Rheumatology is committed to support well-designed IITs that will improve rheumatology patient's care. Such IITs do serve to add to the body of generalizable evidence and advance in rheumatology. IITs are a unique opportunity to contribute to clinical development and research.

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