Biologic National Registry (BINAR) protocol: Design and Rationale of the Tunisian clinical multicentric study of efficacy and safety of biologics in Rheumatoid arthritis and Spondyloarthritis

Protocole du registre national BINAR: Conception d'une étude multicentrique tunisienne sur l'efficacité et la sécurité des biothérapies dans la polyarthrite rhumatoïde et la spondyloarthrite

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Abstract

Introduction: The advent of biological therapies has greatly improved the treatment and management of rheumatoid arthritis (RA) and spondyloarthritis (SpA). However, evaluating the efficacy and long-term safety of these therapies is a necessity. So far in Tunisia, no large prospective multicentric trial reflecting national data has been published. Thus, the objective of the study was to collect data on sociodemographic characteristics of Tunisian patients with RA and SpA receiving biologics and to evaluate the clinical efficacy and safety of this therapy.

Methods: BINAR is a prospective, observational registry with a 2-year follow-up period. A total of 600 consecutive patients treated with biologic for RA or SpA form different regions of Tunisia, are included until the end of the recruitment period, set at one year.

Patients are officially included in BINAR only if they are aged 18 years and older. All patients monitored for RA according to ACR-EULAR criteria or SpA according to ASAS Criteria starting biological treatment at the time of inclusion or within two years before the inclusion date are eligible to be enrolled. All patients provided written informed consent.

The primary end point is the safety and tolerability assessment of biologics and the incidence of adverse events over 2 years. The secondary end points are the assessment of RA and SpA activity at baseline and at two years of follow-up.

Results: One hundred rheumatologists are involved in this study. Ten departments participated in the registry. Demographic profile, activity and disability of RA and SpA will be evaluated. Efficacy and safety of biologic and the incidence of adverse events will be determined at the end of the 2-year follow-up period for every patient.

Conclusion: BINAR is an essential source of clinical efficacy and safety information for biologic agents. It will be a large register for Tunisian patients. This study would add and provide valuable data for the long-term outcome of patients with RA and SpA treated with biologics.

Key words: Biologic; Safety; Efficacy; Rheumatoid Arthritis; Spondyloarthritis; Registry; Tunisia

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Résumé

Introduction: L'avènement des biothérapies a considérablement amélioré le traitement et la gestion de la polyarthrite rhumatoïde (PR) et des spondyloarthrites (SpA). Cependant, l'évaluation de l'efficacité et de la sécurité à long terme de ces thérapies est une nécessité. Jusqu'à présent en Tunisie, aucun essai prospectif multicentrique reflétant les données nationales n'a été publié. D'où l'objectif du registre BINAR (Biologic National Registry) qui était d'évaluer l'efficacité clinique et la sécurité des biothérapies chez des patients tunisiens atteints de PR et de SpA.

Méthodes: BINAR est un registre prospectif et observationnel avec une période de suivi de 2 ans. Un total de 600 patients consécutifs traités par des biologiques pour une PR ou une SpA, provenant de différentes régions de la Tunisie, seront inclus jusqu'à la fin de la période de recrutement, fixée à un an.

Les patients sont inclus dans le registre BINAR s'ils sont âgés de plus de 18 ans. Tous les patients suivis pour une PR selon les critères ACR-EULAR ou pour une SpA selon les critères ASAS et débutant un traitement biologique au moment de l'inclusion sont éligibles à l'étude, de même que ceux qui sont sous biothérapie initiée depuis moins de deux ans avant la date d'inclusion. Tous les patients ont donné leur consentement éclairé par écrit.

Le critère d'évaluation principal est l'évaluation de la sécurité et de la tolérance de la biothérapie. Les critères d'évaluation secondaires sont l'évaluation de l'activité de la maladie au début de l'étude et après deux ans de suivi.

Résultats: Cent rhumatologues ont accepté de participer à cette étude. Dix services de rhumatologie ont été impliqués. Le profil démographique et l'activité de la PR et de la SpA seront évalués. L'efficacité et la sécurité des traitements biologiques et l'incidence des effets indésirables seront déterminées à la fin des deux années de suivi de chaque malade.

Conclusion: BINAR est une source essentielle d'informations sur l'efficacité clinique et la sécurité des agents biologiques. Il s'agit d'un registre important pour les patients tunisiens. Ce registre fournira des données précieuses sur l'évolution à long terme des patients atteints de PR et de SpA traités par des agents biologiques.

Mots clés: Biothérapie ; Sécurité ; Efficacité ; Tolérance ; Polyarthrite rhumatoïde ; Spondyloarthrite ; Registre ; Tunisie

Introduction

One of the most significant advances in the treatment of rheumatic diseases in recent years has been the development of biologics. They may be classified into those inhibiting tumour necrosis factor (anti-TNF), and those targeting other cytokines or cells (non-anti-TNF). Several new biologic agents have emerged with the deepening of exploration and understanding of pathogenesis of rheumatoid arthritis (RA) and spondyloarthritis (SpA) and have been claimed to be effective in randomized controlled trials (RCTs) and observational studies [1,2]. However, these studies are conducted in controlled environments and we must remain vigilant about the long-term tolerability of biologics. The results from trials may not necessarily reflect clinical outcomes in daily clinical practice.

Patient registries are currently being used to provide real-life information on the efficacy and long-term safety of biologics, overcoming the limitations imposed by clinical study methodologies. Numerous biologics registries have been described in different European, Asian, and American countries [3-7]. In North Africa, the Moroccan registry of biological therapies in rheumatic diseases (RBSMR) has already published several results on biologics [8,9]. In Tunisia, there are scant published data on the use of biologics. Clearly, data from international studies and other registries may not always be extrapolated to our population. Thus, BINAR has been established to monitor patients receiving these drugs. In this study, we will discuss the value and rationale for establishing this biologic registry.

Registry Objectives

BINAR is a prospective observational accumulation of data used in the investigation of the optimal management of biologic agents in Tunisian RA and SpA patients and present status of biologics in Tunisia.

The primary outcome measure of BINAR is to evaluate the safety and tolerability of biologics and to describe the incidence of treatment-emergent adverse events such as occurrence of infection or tuberculosis (TB) or death or neoplasia or any other treatment-related side effect of biologics. Initially, monitoring is done every 3 months and then every 6 months up to 2 years.

The secondary outcome measures are RA and SpA activity and the long-term efficacy of the used biologics.

Methods

Study Design and Patient Enrollment

BINAR is a Tunisian, descriptive, non-interventional, multicenter and prospective clinical study performed in rheumatology consultations, of both public and liberal sectors. The enrollment occured all over Tunisia between May 23, 2018, and May 23, 2019. All patients are planned to be followed for two years.

Eligible patients are recruited by consecutive enrolment. Consecutive patients were screened for eligibility at the time of their presentation to a rheumatologist (hospital or medical center).

Patients will be officially enrolled in this register only if they are above 18 years-old. Patients should be followed for RA according to ACR EULAR criteria or SpA including all phenotypes (axial, peripheral, enthesitis) according to ASAS criteria. Biologics such as anti-Tumor necrosis factor alpha (anti-TNF), Rituximab, Tocilizumab should be started at the time of inclusion or should be the first biological treatment initiated within two years prior the inclusion. An informed consent, read and signed must also be obtained.

Exclusion criteria are biologics prescribed as second or third line treatment, evolutionary neoplasia at the time of inclusion, other associated systemic diseases (except Sjögren's Syndrome), consent not obtained and pregnancy or lactation.

Sample Size and Data Collection

The Tunisian national registry is carried out by 100

rheumatologists who have agreed to participate. Ten hospital institutes joined the study with a target of 600 patients for BINAR.

While it was anticipated that most investigators would be hospital-based rheumatologists, recruitment by office-based rheumatologists was allowed if patient follow-up was feasible, defined by access to patient records, adherence to study protocols and availability of required data collection.

A baseline visit was planned, followed by visits at 3 and 6 months, and then every 6 months for 2 years. Enrolment into the registry started on 23 May 2018, with an estimated inclusion period of up to 12 months. All patients are followed for 24months. During this period, all participants consulted their rheumatologists at the usual intervals.

The data collected were managed by the Clinical Suite platform (Dacima Software), which complies with international standards including US Food and Drug Administration 21 Code of Federal Regulations Part 11, US Health Insurance Portability and Accountability Act, International Conference on Harmonisation, and Medical Dictionary for Regulatory Activities. The Clinical Suite platform allowed us to track the data entered, check for inconsistencies and missing data, and schedule monitoring visits. A steering committee was set up to monitor patient inclusions, verify data sources, perform the audit trail, and prepare the statistical analysis plan for the study. Data were collected every 3 months during the first 6 months and then every 6 months up to 2 years of follow-up. All incident events and therapeutic changes were entered at each collection interval.

Baseline data included patient demographics, diagnosis, comorbidities (TB, malignancies, cardiovascular disease...), disease activity scores, functional disability, radiographic damage, extra articular symptoms, immunological status, fatigue scores and quality of life, prior DMARD therapy and prednisolone use, biological treatment with evaluation tolerability and side effects. At follow-up, disease activity, comorbidities, vaccination, concomitant treatment, as well as biological switches and adverse events were recorded. In-depth data regarding biological agents, dosing, discontinuations, and reasons for discontinuations were included in follow-up data.

Timeline

Patient recruitment and data collection are scheduled between May 2018 and May 2019. Follow-up is planned until all patients have 2-years data. Figure 1 describes the study protocol.

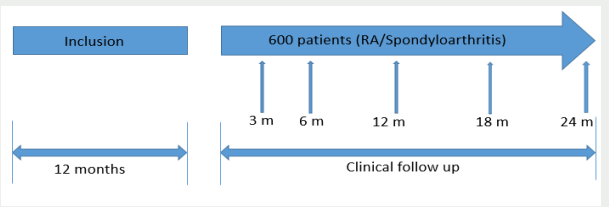

Figure 1. Study protocol

Outcomes

During the follow-up, this observational study aimed to evaluate the efficacy and safety of biologics, as well as to describe the incidence of treatment-related adverse events, such as the occurrence of an infection or TB or neoplasia or death or any other adverse effect of treatment related to biologic agents.

Every serious adverse event (SAE) must be reported. This is defined as any untoward event that, at any dose, leads to death, or is life-threatening, requires hospitalization or prolongs of existing hospitalization. It may also result in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect [10].

Ethical Considerations

Ethics approval was obtained from the Ethics Committee of Mohamed Kassab Orthopedic Institute in Tunis. Informed consent from individual patients was obtained before participation in long-term follow-up. The study was performed according to the ethical principles for medical research involving human subjects specified in the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practices.

Statistical Analysis

Continuous variables will be described by mean and standard deviation or as median and interquartile range. Categorical variables will be described by the size and frequency of every modality. Means comparison will be performed by analysis of variance or by nonparametric tests if the hypothesis of normality is rejected. The normality of continuous variables will be verified with the Shapiro-Wilk test. The statistical tests are bilateral with a 95% confidence interval.

A chi-square test will be performed for categorical variables. Yates correction or the Fisher exact test will be used if the conditions of validity for the chi-square test are not met.

Univariate logistic regression will be carried out with a 10% output threshold. The final model will be performed with the parameters selected by the backward stepwise method of Wald. The selected variables in the final model will be tested at the 5% threshold. The interaction between selected parameters is tested at the 10% threshold.

Expected Implications

The BINAR is the first large-scale investigation to clarify the contemporary demographic data, management of RA and SpA patients, and efficacy and safety of biologic agents in Tunisia.

Oversight and Leadership

The protocol of BINAR was approved by the Tunisian League Against Rheumatism (LITAR). The BINAR study was submitted to ClinicalTrials.gov [NCT03793660].

Study Sponsorship

BINAR is sponsored by the national society of rheumatology: LITAR (Ligue Tunisienne Anti-Rhumatismale).

Results

Results will be available at the end of the study and will be published when the target of 600 patients will be reached. The safety, efficacy and tolerability of the biologics and the incidence of adverse events will be assessed at the end of the 2-year follow-up period for each patient. Patients should be treated with a biologic for RA or SpA at the time of emrolment and the first biologic treatment should have been started for less than two years previously. A Scientific Committee will validate the scientific writing, a Steering Committee will oversee the clinical operations of the project and a Data Review Committee will supervise the data management and perform all tasks related to auditing and checking the validity of the data collected, as well as planning the statistical analysis.

Discussion

Over the past decade, biologic agents had been developed and confirmed to be effective for the treatment of spondyloarthritis [11,12]. Additionally, in RA, clinical trials have shown that biological agents treat many aspects of disease such as suppression of joint inflammation, prevention of radiographic progression, improvement of physical function and health-related quality of life [1]. The increasing use of biologics has generated the necessity of the long-term efficacy and safety evaluation of these therapies.

RCTs do not accurately reflect the use of biologic agents either long-term or in the clinical setting. The RCTs included in the Cochrane database for biologics were short-term, with a median duration of 6 months. As a result, there were an insufficient number of cases of several outcomes (eg, serious infections and malignancy) to make a thorough analysis possible. The Open-Label Extension (OLE) studies were longer in duration and provided risk estimates of TB reactivation. However, it was not possible to evaluate the impact of biologics on serious malignancies and infections [13].

Therefore, registries are necessary to complete the safety data obtained from RCTs and to provide real-life information and the outcome of therapies used in clinical practice. Biologics registries have now been established in several countries. According to a systematic literature review and meta-analyses of biologic registers, some forty registries around the world have been identified. The majority are European, others from North and South America, Asia, one of the Emirates and one from Australia [14]. Most of them were initiated in collaboration with national rheumatology societies and are managed by medical professionals. Some included exclusively RA, others included various chronic inflammatory diseases such as ankylosing spondylitis or psoriatic arthritis. Biologic registers are designed as epidemiological cohort studies for which patients are recruited from clinics or the general population [15]. Despite differences in terms of size, methods of follow-up, and control groups, they provide significant data applicable to an unselected population of patients with RA or SpA treated with biologic in real life [16]. Information collected includes composite indexes, evaluation of effectiveness and adverse events.

Close collaboration between international registries has been possible, allowing evaluation and comparison of data from one register to another. This allowed for a solid knowledge of rare events [17]. To answer many questions about the long-term efficacy and safety of using biologic drugs, these registries have been very useful and were able to provide data on treatment discontinuation rates due to adverse events, incidence of TB, lymphoma and cancer, and the effects of biologics on pregnancy [18-22]. However, differences in safety have been observed, which may depend on the comorbidity profiles of patients included in the registers of a specific country. In addition, baseline rates of opportunistic infections (eg, TB) in the population may play a role in the divergence of reported safety outcomes by region [23]. Therefore, in order to deal with the variations of a specific country, it's important to establish registries around the world.

In the Middle East and Africa, there is a rising trend for the use of biologics in RA and SpA [24]. However, there is a paucity of data on disease activity, treatment, and outcome of patients [25]. As these drugs are used long term, it's important to have robust monitoring and safety assessment measures. Currently, with a limited number of established registries, these countries should to extrapolate available registry and RCT data from other regions. Safety characteristics for biologics reported in the registries discussed may not translate directly to patients from these countries. Multiple factors may lead to discrepancies when comparing registry safety data from different regions. For example, patients may respond differently to biologics due to their genetic background [26]. In the other hand, following available recommendations from international society may be not easy to applicate in our country, due to our lack of resources, non-adherence to biologics by patients [27] or dissatisfaction of the treatment [28].

Therefore, availability of registry data from Africa may help clinicians make informed treatment decisions based on local safety data. Published results from the Morocco registry [8,9] and South African Biologics Registry (SABIO) [29] demonstrate the importance of regional data in understanding the safety and efficacy of biologics. However, these results cannot be directly extrapolated to Tunisia due the differences in genetic, environmental and healthcare factors. In our country, BINAR will provide a unique opportunity to answer many clinical questions. It's a large register allowing the evaluation of biologic treatment management in real-world. Also, systematic observational and outcomes data can be generated from this study and will be used for comparison with different countries and will evaluate

adherence to recent guidelines. This Tunisian study, like all registries [8,23,29,30] will include patients with RA and SpA and will supply long-term data about treatment, thus providing more realistic estimates of the potential risks of biologics.

Conclusion

BINAR, the first national registry on biologics for RA and SpA, will provide unique and necessary real-life efficacy data and will be used to assess the long-term safety of biologic treatment. In Tunisia, there is a paucity of data on the epidemiological characteristics of RA and SpA patients and the management of biologic therapy are available. In addition, with the increasing availability of biologics, there is a clear need to develop a registy to address specific variations in patient profiles.

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