

Experimental Models in Rheumatoid Arthritis: A Systematic Review using the IRAMUTEQ software

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Abstract

Rheumatoid arthritis is an autoimmune and chronic pathological condition characterized by an inflammatory process of the joints. It is a complex and multifactorial, involving genetic, epigenetic and environmental factors and the use of experimental models is required to better understand its pathology and for drug testing. The aim of this study was to perform a systematic literature review on experimental models in rheumatoid arthritis using IRAMUTEQ, a software that analysis, qualitatively and quantitatively, text fragments, as a methodological tool. After searching for articles published in the last five years on Scopus database and applying the exclusion criteria, we ended with 84 articles. The most commonly employed experimental models was the arthritis induction by inoculation of the Complete Freund's

Adjuvant (CFA), followed by the use of combined methodologies and the collagen-induced arthritis (CIA). The analyses of abstracts by the IRAMUTEQ software provided a classification according to their textual elements in four classes, which were grouped into three main themes: *in vivo* models (class 1), clinical practice and traditional medicine (classes 2 and 3) and *in vitro* models (class 4) and it was also possible to build a similarity tree of the terms present in the abstracts and a word cloud with the most cited terms. Thus, the use of the IRAMUTEQ software as a methodological tool has been satisfactory, since it was possible to identify the main experimental models used, keywords, pathological processes and molecules involved in the pathogenesis of rheumatoid arthritis free of the researchers' bias, in addition to being a tool for visual and intuitive results.

Keywords: Rheumatoid arthritis; Experimental models; IRAMUTEQ; Content analysis

1. Introduction

Rheumatoid arthritis is an autoimmune and chronic pathological condition characterized by an inflammatory process of the joints and, with the evolution of the disease, bone and cartilage loss due to fibrovascular infiltration in the affected tissue being responsible for motor impairment if not controlled. Usually the synovitis is installed preferably in small joints (feet and hands), leading to incapacitation of carrier in simple tasks of daily life if not controlled.

The pathogenesis of rheumatoid arthritis is complex and multifactorial, involving genetic, epigenetic and environmental factors. Despite the drugs available present positive effects in disease control for most of the population, diseases of autoimmune nature continue to be a vast field of research to the elucidation of pathophysiology and search for alternative therapies for better control of the disease. Central aspect of the pathogenesis is the activation of macrophages by autoreactive T cells resulting in the production of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- α) and interleukins 1, 6 and 17 [1], [2]. According to Caplazi et al. [3], therapeutic strategies and research has addressed the immunotherapies that targets the inflammatory cytokines and/or their receptors, the events that trigger the generation and recruitment of autoreactive T cells, the role of antigenic variants of autoreactive T cells against citrullinated antigens and the presence of citrullinated antibodies, which has been linked to the development and progression of autoimmune diseases [4].

Although also affects the joints as well as causes the symptoms of chronic inflammation, leading to cartilage and bone loss, osteoarthritis has big differences when compared to rheumatoid arthritis and cannot be studied and treated the same way. Both are inflammatory manifestations in the joints, but while osteoarthritis is induced by multifactorial mechanisms triggered basically by biomechanical stress in a particular joint, rheumatoid arthritis is triggered by a systemic autoimmune process that affects multiple joints at the same time to bilateral way and is characterized by a chronic inflammation that manifests itself in cycles of activity and remission. Due its autoimmune origin, the rheumatoid arthritis also carries with it some comorbidities, such as cardiovascular problems related to the formation of atherosclerotic plaques, higher risk of developing tumors and immune dysfunctions, increasing the risk of bacterial, viral and fungal infections [5], [6], [7].

Besides the difference regarding the pathogenesis, recent researches have shown epigenetic differences,

involving patterns of histone acetylation and methylation, expression patterns of serum inflammatory cytokines and matrix metalloproteases, different patterns of oral microbiota and distinct secretory activity in the joint and subcutaneous adipose tissue [6], [7], [8], [9], [10].

The IRAMUTEQ (Interface de R pour l'Analyse Multidimensionnelle de Textes et de Questionnaires), a textual content analysis software created by Frenchman Pierre Ratinaud, uses the Python language and makes use of statistical tools of the R software, which promotes an impartial and optimized analysis of textual content to address a given topic to be studied, in addition to providing you with the results in the form of dendrograms, similarity trees and word clouds [11].

The analysis is based on the concept of descendence hierarchical classification (DHC), which sorts the text segments on the basis of their respective vocabularies. This classification aims at obtaining classes of elementary context units (ECU) which includes the amount and average frequency of words in different texts. Therefore, within the same class, the ECU presents similar vocabulary to each other, and a different vocabulary if compared to the ECU from other generated classes. It is also possible to be made a factorial correspondence analysis (FCA) from the DHC, which allows us to analyze the statistically most significant words of each generated class plotted on a cartesian plane [12].

It is scarce the amount of scientific articles that have made use of this methodology for research on systematization of a literature review, but we can highlight the work of Broc et al. [13], in which the qualitative analysis of the opinion of surgeons in order to find out the factors that influenced significantly the decision-making process of these professionals in the treatment of patients with colorectal tumors. After analysis, it was possible the separation of the factors influencing decision making in five different classes (factors related to the opinion/desire of the patient, prior knowledge of the surgeon, aspects of treatment, tumor aspects and organizational aspects) and it was observed that all the criteria for a decision, biomedical (tumor) or heuristics (experience of the surgeon), converged to a single central factor (age) in the analysis of similarity. That way, they could propose an explanatory model where it was possible to check how heuristic factors impacted on medical affairs (diagnosis, prognosis and treatment) and, consequently, in decision making.

Another aspect that can be addressed by using the software as a methodological tool is the identification of central lexical items and their peripheral system on similarity analysis. Thus, from the verification of the connectedness of the terms, it is possible to infer which co-occur in terms more often and, from this premise, make use of these terms as a guide for the preparation of revisions of a particular topic of interest. The more branched the similarity tree generated is, will be the broadest web of interrelations on a determining issue [14].

In the light of the stated above, our goal was to perform a systematic search of the literature on experimental models in rheumatoid arthritis using IRAMUTEQ software as a methodological tool.

2. Methodology

Articles published between 2014 and 2018 and indexed in Scopus platform using the directories "rheumat* arthritis" [AND] "experiment* model" were selected according to the following exclusion criteria: (a) review articles; (b) absence of abstract available; and (c) other pathological condition addressed.

For textual content analysis, we used the IRAMUTEQ software (Interface de R pour l'Analyse Multidimensionnelle de Textes et de Questionnaires), which did the analysis of the articles' abstracts that were grouped into a single file in text format (.txt), called textual corpus. For each abstract, have been assigned the following identification directories: first author of the article and experimental model used. By being connected to the software platform of R, it was possible the analysis of multivariate and content as the frequency of words, factorial analysis of correspondence of word classes and the directories used, analysis of similarity and word cloud, enabling a qualitative and quantitative analysis of the abstracts.

3. Results and Discussion

The search for articles in Scopus platform that were involved in research about rheumatoid arthritis using experimental models resulted in a total of 112 articles published between 2014 and 2018. Among this total, 28 were excluded from subsequent analysis articles, where 19 of them were about other pathological conditions, 8 were reviews of literature and 1 did not contain abstract available, totaling 84 articles for review of abstracts through the software IRAMUTEQ (Figure 1).

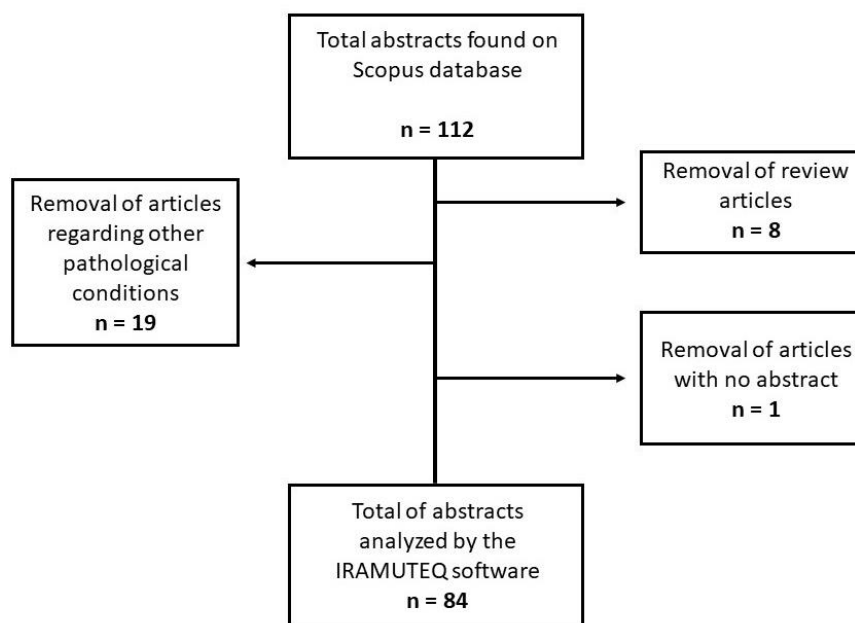


Figure 1. Flow diagram regarding the selection process of the articles on “rheumatoid arthritis” and “experimental models” searched on Scopus database and published between 2014 and 2018.

When it comes to the experimental models employed in the development of research in rheumatoid arthritis, the most commonly employed are the induction by inoculation of the Complete Freund's Adjuvant (CFA), accounting for 31% of the abstracts surveyed, followed by the collagen-induced arthritis (CIA), present in 18% of the abstracts surveyed. Most of the researches are also carried out using combined methodologies, i.e. more than one type of induction, named in our research as multiple methods (mult), accounting for 26% of the surveyed abstracts. (Figure 2).

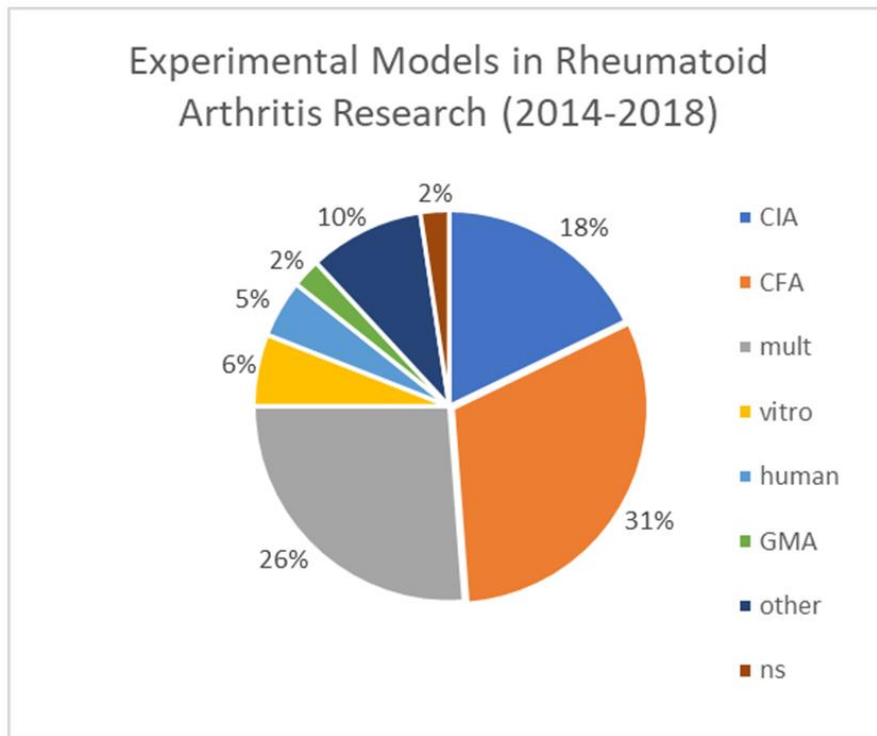


Figure 2. Frequency of the experimental models used on rheumatoid arthritis research in published abstracts on Scopus database between 2014 and 2018 (n=84).

CIA: Collagen-induced arthritis. CFA: Complete Freund’s Adjuvant. Mult: multiple models Vitro: in vitro models. Human: use of patients’ samples. GMA: Genetic modified animals. Other: other models. NS: Non-specified.

The textual content segmented and analyzed by DHC is represented in the form of a dendrogram, where we can observe the stratification of the textual elements in four distinct classes and, within each class, the terms with the highest occurrence (Figure 3). This representation allows us to infer the distance between textual content, being the class 1 more distinct and the classes 2 and 3 closer to each other. This proximity and even interrelationship can also be visually observed on the cartesian plane representation of the FCA (Figure 4).

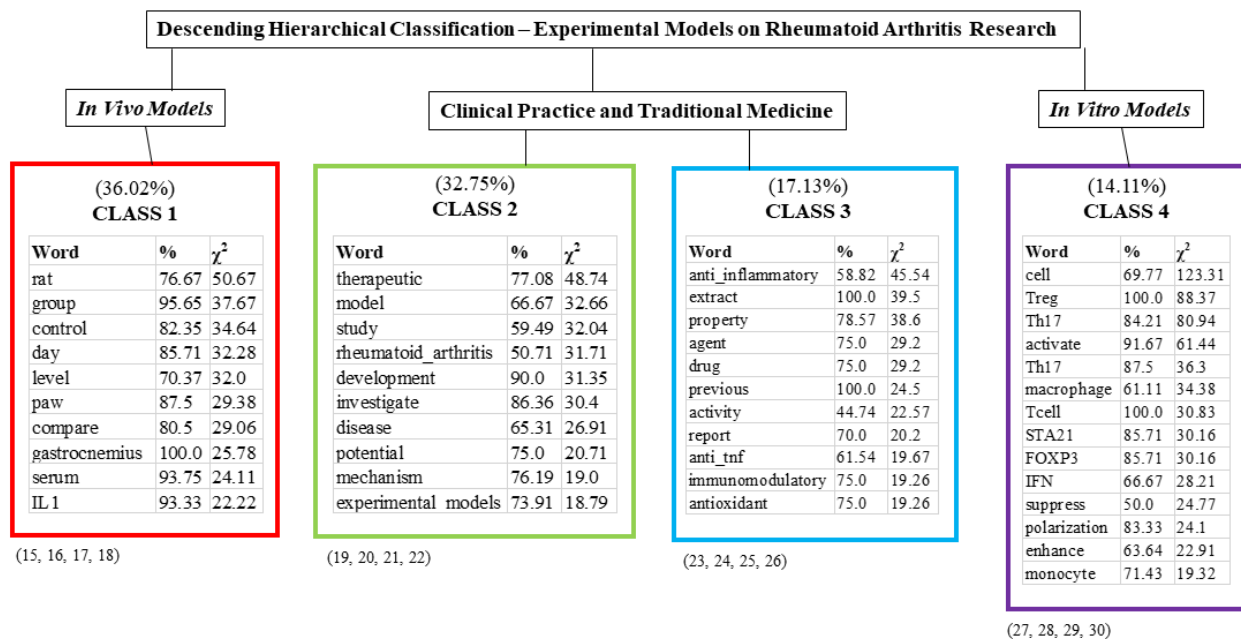


Figure 3. Dendrogram of the Descending Hierarchical Classification (DHC) with the percentage of Elementary Context Units (ECU) of each class.

Words with greater chi-square and abstracts classified in each class provided by the IRAMUTEQ software, 2019.

The representation of the FCA in a cartesian plane makes the separation of the classes intuitive and practical, so that we can visually identify the class 1 and class 4 more clearly separated from the other two remaining classes, which are visually connected, and can be considered as a single class. In this representation you can also view the terms that have high frequency (greater qui square) within each class; most frequently terms are represented in major fonts and, less frequently, in smaller fonts (Figure 4a).

When interpreting the results from the DHC and FCA, it was able to name the main areas of study of the research topic. The class 1 stick with the terms relating to the use of model experiments in animals, such as: rat, group, control, day, level and paw. The classes 2 and 3, which may be grouped together due to the apparent overlap of their terms in the FCA, made use of terms referring to the epidemiological characteristics, clinical and observational data, the main ones being: therapeutic, model, study, potential, anti-inflammatory, extract, property, drug, among others. The class has 4 terms of Immunology and areas of cultivation of cells to investigate the modulation and control of serum levels of biomarkers such as interleukins and Cytokines and comparing the effect of therapeutic targets in the increase or decrease of these factors, correlating them. We can also observe the use of alternative models, in vitro techniques and genomic analysis, proteomics and biotechnology for the great quote of terms such as: cell, Treg (T regulator lymphocyte), Th17 and Th1 (T helper lymphocytes responsible for production of interleukins 1 and 17), macrophage, IFN (interferon), mesenchymal stem cells, polarization, production, proliferation, among others. Thus, it was possible the correlation of the themes of these generated classes (1-in vivo Models 2 and 3-extrapolation of experimental data for clinical practice and use of medicinal plants and 4-in vitro Models) with some of the abstracts researched and experimental models used (Figure 4b).

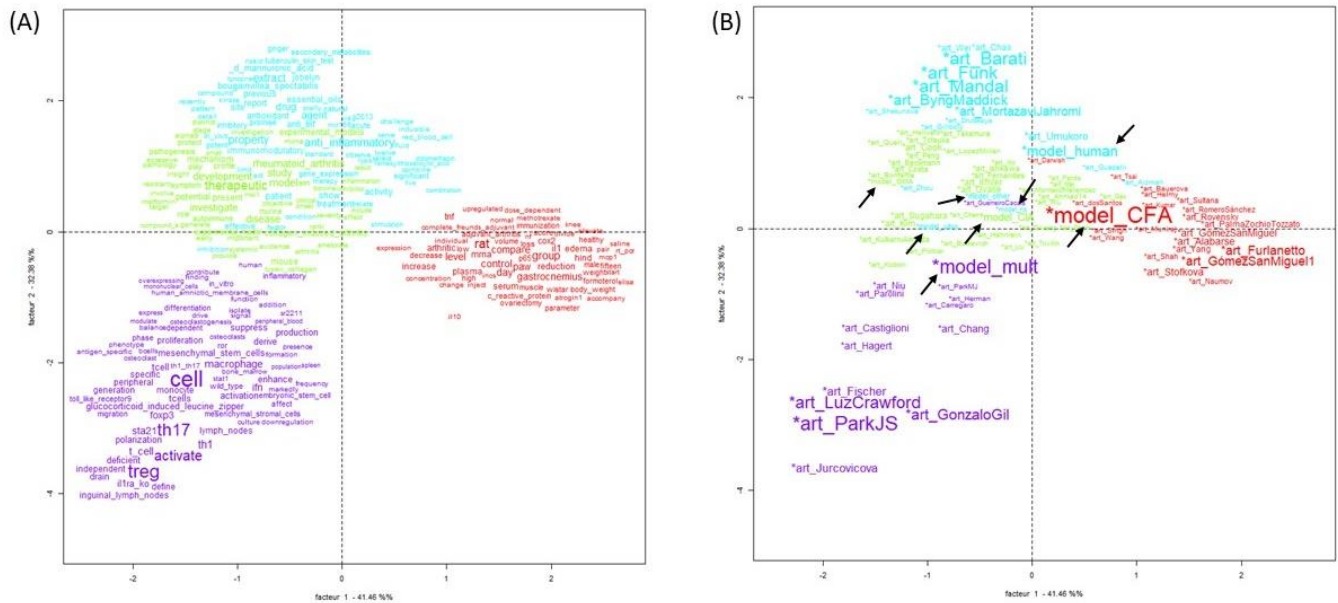


Figure 4. (A) Factorial representation generated from the DHC of the ECU provided by IRAMUTEQ software. (B) Factorial representation generated from the DHC of the directories attributed on the analyzed abstracts (n=84) provided by IRAMUTEQ software, 2019.

Circles: experimental model. CIA: Collagen-induced arthritis. CFA: Complete Freund’s Adjuvant. Mult: multiple models Vitro: in vitro models. Human: use of patients’ samples. GMA: Genetic modified animals. Other: other models. NS: Non-specified.

Despite the experimental models be sorted by the software as belonging to different classes and since they are more widely used to meet grouped around the center of the cartesian axis, not necessarily the articles classified in the same class of a particular experimental model, will present the use of this model. It is worth noting that the software makes the classification according to the textual corpus of each abstract, bringing articles to a particular experimental model due to language and terms employed.

The similarity analysis is based on graph theory and identifies the co-occurrence between words in a text segment, indicating the connectedness between words with greater frequency in the abstracts. The analysis result is obtained in a graphical format of a tree formed by the lexical items, the central topic of research, and peripheral items attached to it. The closer a lexical item to another, closer are in same text segment, and the more branched perform similarity tree, widest is the interrelation of the terms and the search object [12].

The similarity tree generated in our review of the literature does not have many branches, being almost linear, which demonstrates the robustness in the scientific method of investigation of rheumatoid arthritis by research groups from different places in the world. The software was able to identify the central theme of the research, rheumatoid arthritis, experimental models mostly used by researchers, induction by collagen type 2 and use of Freund's complete adjuvant (adjuvant arthritis), key issues in the pathogenesis as the terms joint, chronic, autoimmune, inflammatory, macrophage, TNF (Tumor Necrosis Factor), cytokines, and terms related to the scientific methodology to develop in vivo models, as the animals used,

verification of the connectedness between words, it was possible to identify the central theme of the research and its main developments (Table 1).

Table 1. Identification of the central theme, peripheral themes and their developments in the similitude tree generated from IRAMUTEQ software, 2019.

CENTRAL THEME	PERIPHERAL THEMES	DEVELOPMENTS	STEP OF THE STUDY
Rheumatoid Arthritis	Disease	Autoimmune	Background
	Effect	Activity	
		Anti-inflammatory	
	Joint	-	
	Patient	-	
	Macrophage	-	
	Inflammation	-	
	Cytokines	-	
	TNF (Tumor Necrosis Factor)	-	
	Experimental Model	-	
	Response	-	
	Study	Evaluate	Methodology
		Determine	
	Mouse	Collagen-induced Arthritis	
		Treat	
		Suppress	
	Cell	Production	
		Mesenchymal Stem Cells	
	Rat	Adjuvant Arthritis	
		Induce	
	Expression Level	Increase / Decrease	
Reduce			
Compare	Significantly		
	Inhibit		
	Paw (edema)		
	Group		
	Control		

Also as part of the review of abstracts by IRAMUTEQ software, it was generated a wordcloud in which the terms with greater frequency are organized graphically, allowing rapid identification of keywords of a set of texts. The bigger the font and more centered on the cloud, the greater the frequency of the word (Figure 6).

In this way, we can identify around the topic of research, rheumatoid arthritis, the terms related to the main

and intuitive results.

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7. Competing Interests

The authors declare no competing interests.

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