

RESEARCH ARTICLE

MALE RHEUMATOID ARTHRITIS IN ALL MOROCCAN RA UNDERGOING BIOTHERAPY: PREVALENCE, CHARACTERISTICS, AND RESPONSE TO BIOLOGICAL TREATMENTS (NATIONAL REGISTRY)

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Manuscript Info Abstract Manuscript History Introduction: This study aims at reporting the RA male frequency

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Key words:-

Rheumatid Artheritis, Gender, Biotherapy **Introduction:**This study aims at reporting the RA male frequency while undergoing biotherapy and describing the epidemiological characteristics (clinical, biological and radiological) in relation to female RA. It also evaluates its impact on the response to biological treatments.

Materials and methods: There are 224 patients followed for rheumatoid arthritis, responding to ACR/EULAR 2010 criteria during their biotherapy. They were included in the national "RBSMR" registry. The patients were divided into two groups and were compared at the basis of their gender in terms of the socio-demographic, clinical, biological, radiological parameters, and response to the treatement.

Results: The average age of the patients under study is 51.94 ans ± 11.36 years old [20-80]. The presence of male rheumatoid arthritis under biotherapy is 12.4%. The mean age of RA male is 55.96+9 years old. The estimated duration of progression of male RA is 542 weeks with an average diagnostic deadline of 562.61 weeks.

As a description of the case study, 28,6% of men are diagnosed with cormobidities (mainly tuberculosis 21.4%) while 10,7% of men are smokers. There is an average sedimentation rate (1st hour) at 52.6mm.

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Rheumatoid serology is found to be positive in 96.4% of cases. Radiological abnormalities are observed in 90.5% of the cases. Male rheumatoid arthritis is related to a shorter duration of progression (542 versus 768 weeks in females, p=0.01), liberal profession (p=0.00), study level (p=0.003), duration between diagnosis and the starting of biotherapy (p=0.021), EVA pain patient and physician (p=0.003, p=0.01) Tobacco (p=0.006), and pulmonary tuberculosis (p=0.029). On the other hand, it was not associated with the following parameters: age, duration of diagnosis, disease intensity, rheumatoid serology, structural damage nor with the DAS 28vs response during one year. **Conclusion:** The male RA rate in RBSMR study is 12.4% in that there is no significant difference between the sexes in clinical presentation, disease activity, disease severity, rheumatoid serology and response to the biotherapy. However, male RA was related to smoking, liberal

profession, and history or occurrence of pulmonary tuberculosis.

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Introduction:-

Rheumatoid arthritis (RA) is the most commonly known chronic inflammatory rheumatic disease, affecting women four times more than men (From 35 to 55 years old). Historically speaking, researches have already shown interest in studying this disease in relation to the issue of gender. In fact, various published works come the conclusion that there is difference between the two sexes while being diagnosed with RA in terms of prevalence, age at the beginning of the disease and auto-antibody positivity [1]. Similarly, the evolution of female RA is severe compared to male RA.

Practically speaking, rheumatologists do not pay much attention to the patients gender. However, sientific development proves to be unexpected. Hence,male sex has been shown as major predector factor of remission in early RA [2,3]. Some studies suggest that males respond positively to the biological treatment in comparison to females [4–6].

In this study, we want, mainly, to report the male RA prevalence while undergoing a biological treatment (refractory to CsDMARDS) through describing its clinical and paraclinical profile and comparing it to the female RA. Then, we compare how both males and females respond to the biological treatment.

Materials And Methods:-

This is a multi-center group study that includes 10 rheumatology departments in university hospitals in Morocco : Agadir, Casablanca, Fez, Marrakech, Meknes, Rabat, Sale and Oujda.

The sponsor is the Moroccan Society of Rheumatology (SMR). This study involves 224 patients who are older than 18 years of age, treated from RA, meeting ACR/EULAR 2010 criteria on biotherapy (or who have received an infusion of rituximab within the last 12 months.) These patients are included in the national database that is closed at the end of January 2019. And a second database from this registry includes biologic response data after 6 and 12 months of inclusion, "RBSMR study" data frozen at one year.

The first step, we followed, is that we reported the male RA prevalence within the RA population included in the national biotherapy database. After that, we divided the patients into two groups : Male and female RA patients in order to compare their socio-economic, epidemiological, clinical, biological, radiological, and disease severity characteristics. However, the disease evolution and the patients' response to the treatment were not analyzed because the patients were in the first phase of inclusion.

The second step revolved around comparing the patients response to the biological treatment in male and female RA using the primary criterion of judgment: DAS28VS and the secondary criterion: EVA pain, EVA fatigue, joint index, synovial index, and CRP (the absence of inflammatory syndrome was judged on a CRP less than or equal to 6mg/l).

Using SPSS (Statistical Package for the Social Sciences) version13 software, a comprehensive description of the opulation under study (frequencies and means plus standard deviation) is given. A bi- and multi-varied analysis was conducted using statistical tests (the chi-square test, the Student's T-test for independent sample and a multi-varied logistic regression test), comparing the characteristics of male versus female RA patients. The significant threshold was set at p<0.05.

Results:-

The average age of the population of 224 RA patients was 51.94 ± 11.36 years old [20-80], divided into 28 men and 196 women. The average age of male RA patients was 55.96 ± 9 years old while that of female RA patients was 51.37 ± 11 years old. The prevalence of male RA was 12.5% (versus 87.4% female RA).

The characteristics of the population under study is as follows. 85.72% of men were married compared to 70.1% of women. Also, 35.7% of the men were illiterate compared to 48.2% of women. For work, 60% of men had a liberal profession: commerce, handicraft, etc. (compared to 2% of the women) while 83.2% of the women were housewives. For health services, 50% of the men had FAR social security coverage and 35.7% had RAMED social assistance, while 30% of the women had FAR health insurance and 43.1% had RAMED. The average PR duration progress for males was 542 weeks in comparison to 768 weeks for females, with an average diagnostic period of 562.61 weeks for men versus 767.19 weeks for women. Comorbidities were observed in 28.6% of men versus 36.0% of women. One of the most common comorbidities for men is tuberculosis (21.4%) versus 7.4% for women). 10.7% of men were smokers versus 0.5% of women. We found an average sedimentation rate of 52.6mm during the first hour for men versus 40.3mm for women. Rheumatoid serology (rheumatoid factor and/or ACPA) was positive in 96.4% of males RA versus 94.1% of females RA . The average DAS 28 (CRP) was 4.06 versus 3.51 for women. Mean HAQ was 1.17 for men versus 1.23 for women. Radiological abnormalities were observed in 90.5% of cases versus 92.8% for RA females. The use of orthopedic surgery (arthrodesis and joint replacements including MCP/MTP) was noticed in 3.6% of male RA patients versus 7.1% of female ones. (Table 1).

53,8% of men had a DAS 28VS that is superior than 3,2 versus 68,27% of women. After one-year treatment, 65% of male RA patients showed good results (remission or low disease activity (LDA)) according to the primary outcome of our study (DAS28 vs.) versus 52.21% of women. EULAR response (delta DAS28VS. between admission and 12-month visit) 55.55% of men were responsive or had a moderate response vs. 58.95% of women. The CRP was high in 62.29% of men versus 65.64% of women. After 12 months of biologic treatment, 56.52% of male RA patients had a positive CRP response versus 53.69% of women. A biologic treatment maintenance rate is of 81.2% in men versus 86.7% in women. 3.6% of men had developed side-effects to biologic treatments versus 13.8% of women (p=0.1). (figure 1)

According to the bivariate analysis, the male RA disease is associated to an evolutionary duration that is less important (p=0,01), liberal profession (p=0.00), low educational level (p=0.003), short duration between diagnosis and the starting of biotherapy (p=0.021), extensive patient-physician pain EVA (p=0.003, p=0.01), smoking (p=0.006), and the occurrence of pulmonary tuberculosis during biotherapy (p=0.029), but was not associated with age, diagnosis duration, and structural abnormality (Table 2). Multivariate regression analysis mentioned that there is a relation between male RA and the following criteria : smoking, occupation, and the appearance or history of pulmonary tuberculosis.

In our study, the bivariate statistical analysis did not reveal that responding to the treatment is affected by the male impact for either the primary criterion: DAS 28VS (p=0.455), or the secondary ones: EULAR response (p=0.572), CRP (p=0.123), EVA pain (p=0.23), HAQ(p=0.533).

Discussion:-

Rheumatoid arthritis is a common disease which touches 0.7% of the population (about 200,000 patients in Morocco). It mainly affects women, no matter the ethnic group or the country they come from, with an average sex ratio of 3 women per man. In our research, male rheumatoid arthritis treated with biotherapy represents 12.4% (versus 87.6% of female rheumatoid arthritis), i.e. less than one eighth of all RA treated with biotherapy, making a sex ratio of 7 women per man. A Latin American study by Barragán-Martínez et al, discovered a sex ratio of 5.2 females per male and a prevalence of male RA of 16.1% among 1128 rheumatoid arthritis patients [9]. This

statistical difference can be explained by the specificities of each study. Our study, which focused solely on patients with rheumatoid arthritis undergoing biological treatment, found a lower presence of rheumatoid arthritis than that found by the authors of the Latin American study [9]. This result can be explained by the fact that women have more severe RA and a high risk of being treated with biotherapy.

The RA characteristics also appear to be influenced by gender. In our study, female RA undergoing biologic treatments were younger than males (51 years old versus 55.96 years old), with a shorter period of time to positive diagnosis in males (562.61 weeks versus 767.19 weeks). On the one hand, our findings are consistent with those of Voulgari et al [10] including 454 RA patients, and show a significantly higher mean age of male patients than female ones (55 years old versus 49 years old, p=0.0003).

On the other hand, the diagnostic period was reduced for men (0,3 an vs 0.6 an) in a non-statistically significant way. In the same vein, Barragán-Martínez et al. found that women with RA are younger than men (38.07 years old vs. 42.99 years old; P=0.0001) without specifying the type of treatment these patients undergo. The younger age of RA female compared to RA male is strongly influenced by the role of endocrine factors and the involvement of sexual hormones. This becomes more frequent in the time period between puberty and menopause. Men are rarely affected at a young age, so androgens seem to remove the disease. EVA pain and fatigue, joint index, swollen joint index are slightly higher in men than women. All these characteristics are not statistically significant, therefore gender does not have a greater influence on the clinical presentation of RA. The rheumatoid arthritis severity can be assessed on the presence of an inflammatory syndrome, positive rheumatoid serology, the extent of joint damage observed on X-ray images, Doppler activity on ultrasound of synovitis and erosions, the extent of functional disability, smoking, or the occurrence of extra-articular manifestations. There is a 2% difference in the positivity of rheumatoid serology (rheumatoid factor and ACPA) between men and women. This difference in our study could be explained by :

- 1. The high consumption of tobacco by men (10.7% versus 0.5% of female RA (p=0.006).); known to be associated with rheumatoid factor production and citrullination.
- 2. The inflammatory syndrome is high for men,
- 3. The disease activity is high (DAS28) for men.

However, HAQ, comorbidities, and radiological abnormalities are more prevalent in female RA.

Several studies have come up with the same finding [9,12]. That is to say, despite having an inflammatory syndrome and a positivite rheumatoid serolog, y men had a lower risk of severe joint abnormality than women. In the same vein, Tuulikki Sokka, in his study the QUEST-RA [11], pinpointed at the importance and frequency of erosions in female RA (64.3% versus 59.7%, p=0.003). This paradox between the importance of the inflammatory syndrome in men and the decreased joint destruction in male RA appears to be related to the longer duration of the disease evolution. As is explained in our study, it was 768 weeks for women and 542 weeks for men. In contrast, Weyand et al [12] found erosive RA early and more frequently in men. The same results were also found by Maarten Boers [13] with the same smoking patterns in both sexes.

Based on these data, the QUEST-RA study indicates that measures of disease activity are higher in women than men for DAS28, EVA fatigue, and number of swollen joints. Thus, this study suggests that caution must be taken into consideration when interpreting the level of disease activity since sexe interferes. As reported Misbah Vaqar Patoli, the severity of rheumatoid arthritis in both sexes is variable and age-dependent as reported [14]. The influence of gender on RA characteristics differs from one study to another. In our study, male sex had a minor impact on the presentation of RA, but this influence was not statistically significant.

The period between positive diagnosis and the starting of biologic treatment is reduced for men compared to women diagnosed with RA. This short time period, in our study, is due to either disease severity, significant inflammatory syndrome and high disease activity in men compared to women, (Table 1) or resistance to conventional DMARDS therapy. According to the Dutch report, women were referred late after the onset of symptoms to specialized arthritis clinics compared to men, and consequently there was a long period of time between the appearance of symptoms and the introduction of substantive treatment [15]. In our study, male RA was not statistically related to response to biologic therapies on either the primary crietria (DAS28vs disease activity) or secondary criteria (EULAR response, biological inflammatory syndrome, EVA pain). Consequently, gender does not have an impact on the response to

biological treatment. These results are in line with those found in the literature, particularly in the European studies and the Latin American study where 28.7% of women were under biologic treatment versus 27.1% of men (115).

The RA chronic inflammation is not only limited to the joints, but also affects other organs. In this respect, the prevalence of comorbidities can be altered by the gender of the patients. In our analysis; at inclusion; comorbidities (diabetes, hypertension, obesity, hypercholesterolemia, depression, osteoporosis.) affected women more than men (Table 2). On the other hand, the presence or occurrence of pulmonary tuberculosis is more frequent in male RA (p=0.023). At 12 months on biologic treatment, the appearance of comorbidities was still more frequent in women than in men, but not statistically significant (p=0.144). Two studies by DA Silva [16] in 1992 and Burmester [17] in 2007 found a direct association between the occurrence of severe infection and early mortality in male RA.

With regard to the psychosocial impact, one must be aware of the socio-economic profile of RA patients, especially after the advent of expensive biological treatments. At the time of inclusion, the majority of patients were married, and the divorce rate was the same for both sexes. Professional occupation (manual work, trade...) was statistically related to male RA (p=0.000). Rkain et al [18] found that 42.5% of female RA patients experienced various aspects of abuse from their husbands. Divorce was statistically related to the following parameters: the young age of the patients and the low number of children. Work withdrawal was related to gender: men stopped working more frequently than women (90.9 vs. 52.2%; p = 0.02); age: subjects who stopped working were older than those who were working (48 vs. 41 years old; p = 0.04) and to the nature of work, citing patients who were working in a labour-intensive occupation (100 vs. 29.4%; p < 0.001) and patients doing manual work (75 vs. 16.7%; p = 0.01).

	Men (n=28)	Female(n=196)	P value
Âge(years)	55,96+9	51,37 +11	0.344
Educationallevel	35,7% primary study	48,2% illeterate.	0.003
	32,1% secondary study	21,8% secondary study	
	14,3% illeterate	16,2% primary study	
	17,9% high education	8,6% high education	
	_	5,1% unknown	
Marital status	85,72% Married	70,1% Married	0,372
	7,14% single	13,2% single	
	7,14% divorced	7,1% divorced	
		9,1% widow	
		0,5% NSP	
Type of	50,0% FAR,	43,1% RAMED,	0.339
healthinsurance	42,9% Ramed	30,5% FAR	
Profession	35,7% officiel	83,2% housewife.	0.00
	60,0% liberal.		

Tableau 1:- socio-demographic description of the RA population under biotherapy included in the Rbsmr.

FAR : royal army forces, PR : Rheumatoid arthritis, RAMED : medicale assistance. NSP: no response.

 Table 2:- clinical, biological and radiological characteristics of RA patients undergoing biotherapy (RBSMR) according to gender

	Men (n=28)	Female (n=196)	P value
Average duration of PR evolution	542 weeks	768 weeks	0.01
Diagnostic delay	562,61 weeks	767,19 weeks	0.534
Time between thestart of biotherapy and dg	304 weeks	714 weeks	0.021
Nombre d'articulation gonflé moyen	9,5	7,5	0,715
(introduction biologique)			
Tabac	10,7%	0,5%	0,006
IA: articular index	16	13	0,363
ESR (biological introduction)	52,6	40,6	0.042
CRP (biological introduction)	33.4	28,6	0,565

EVA pain (biological introduction)	7	6,73	0.003
EVAwearness (biological introduction)	6,3	6,4	0,715
BMI	25,6	27,86	0.54
DAS CRP (biological introduction)	4,06	3,51	,055
HAQ	1,17	1,23	0,062
Radiological destruction	90,5%	92,8%	0,143
Comorbidities:	28,6%	36,0%	0,29
pulmonary TB			
Fibromyalgia	21,4%	7,4%	0,029
Depression Hypercholesterolemia	0,0%	1,1%	0,75
Heart disease	7,1%	5,1%	0,455
Diabetes	7,1%	13.3%	0,285
HTA	3,6%	3,1%	0,613
Vasculitis	17,9%	20,9%	0,465
Cancer	7,1%	17,9%	0,119
Osteoporosis	3,6	7,6	0,388
	3,6	0	0,124
	10,71	24	0.120
Past of RA surgical	3,6%	7,1%	0,419
Rheumatoïdserology positive (RF et ou AC	96,4%	94,1%	0,522
anti CCP)			

RA: rheumatoid arthritis, FR: rheumatoid factor, HTA: arterial hypertension, TB: tuberculosis, HAQ: health assessment questionnaire, DAS: disease activity score, BMI: body mass index. EVA: visual analog scale, ESR :Erythrocyt sedimentation rate,





CRP (Average) : protéine C réactive. EVA patient (average), DAS 28 ESR : disease activity score H: men, F:female

Conclusion:-

12.4% represents the prevalence of male rheumatoid arthritis in the RBSMR study including RA patients on biotherapy. This study did not show significant gender differences in clinical presentation, disease activity, disease

severity, rheumatoid serology and response to biologic treatments after one year. In contrast, male RA was associated with smoking, occupation, and history or occurrence of pulmonary tuberculosis.

Declaration of links of interest

The authors declare that they have no links of interest.

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Ethics approval

The protocol for the original RBSMR study was reviewed and approved by local institutional review boards and the national ethic committee.

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