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RESEARCH ARTICLE

A RETROSPECTIVE ANALYSIS OF GLUCORTICOSTEROIDS UTILIZATIONAMONG PATIENTS WITHRHEUMATOID ARTHRITIS

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Abstract

Background: Glucocorticoid therapy is used widely in patients with rheumatoid arthritis(RA). Recently, treatment guidelines recommendglucorticosteroids (GCs) use in low dose and for a short time in RA. However, for many patients, it is still difficult to withdraw GCs once initiated.

Objectives: to analyzeGCs utilization in RA patients and to evaluate the effects of increasing cumulativedoses on theprevalence of potential GCs related adverse events.

Methods:we enrolled patients with RA. Corticoid exposure was defined: duration (short ≤6 months and long >6months), average daily dose (low ≤ 2.5mg, medium 2.5mg < ≤ 7.5mg and high > 7.5mg).
Effect of increasing cumulative GCs doses on adverse events development were analyzed usingchi-square test or Fischer's exact test. Regression models were used to identify the factors favoring GCs discontinuation.

Results:a total of 168 RA were included (84 patients usedbDMARDs). The median of cumulative GCs dose was 14400mg. the majority of GCs users were prescribed high doseof GCs (54.3%) for a long duration (98.7%). Skin events (71.5%) were the majorside effects. Higher cumulative GCs doses compared with lower doses had increased incidence of diabetes, cardiovascular and ophthalmologic events (p=0.04, p=0.001, p=0.02 respectively).The prevalence of RA patients having withdrawnGCs was 38.7%. It was negatively associated in multivariable regression with RA duration (OR:0.8, IC95%:0.6-0.9). Surprisingly, there was no association in logistic regression with bDMARD use.

Conclusions:GCs were used with high dose and for a long duration for the majority of our RA patients.

Introduction:-

Glucorticosteroids (GCs)are commonly used in the management of rheumatoid arthritis (RA) since 1950 due to their powerful anti-inflammatory propertiesand to their structural effect in reducing radiologic progression in early active RA(1_5).However, their use may be limited by the possible occurrence of some deleteriousside effects(2,6,7).

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The American College of Rheumatology(ACR)2015,European League Against Rheumatism (EULAR) 2019 and French Society for Rheumatology (SFR) 2019guidelines for managing RA recommend the lowest cumulative dosage of GCs by usingthe lowest possible dose for the shortest possible duration (3-6 months)(8_10).However, mostpatients seem currentlyto use GCs much longer(2). Thus, weaning GCs once they are initiated is stilla serious challenge in many patients(5,11).

This current study set out to analyzethe use of GCs therapy in RA patients,to determine factors favoring GCs cessationand to assess the effects of increasing cumulative doses on the prevalence of potential GCs related adverse events.

Methods:-

Study

Patients with RA were recruited in our retrospective study from the out clinic of our rheumatology department from May 2020 to December 2020. Data collected based on the medical record of individual patients.

The study population was patients having at least two diagnosis of RAon different dates to increase the likelihood of selecting true patients with RA. We excluded patients with ≥ 1 non diagnostic claim with a diagnosis of any other autoimmune disease.

Patients were required to have at least 10 months of RAprogression.

+GCs exposure:

The GCs exposure in our study included all oral GCs use. Intravenous, intra articular and inhaled GCs were not considered as GCs exposure.

GCs use measures were the timing of GCs use (current use, former use orno use),average daily GCs dosage, GCs duration and cumulative GCs dose.

Former use was defined as at least 3 months after the last dose of GCs, and current use as a last GC use within the last 3 months whiletreatment duration was defined as short term (≤6 months) and long term (>6months). Average daily GCs dosage was calculated by dividing cumulative GCs dose by the number of GCs days exposure and defined as low (≤2.5mg), medium (2.5mg < ≤ 7.5mg) and high (> 7.5mg)(12).

All GCs were converted to a prednisone equivalent dose.

Cumulative GCs doses were categorized into 4 groups: (1) ≤7500 mg; (2) > 7500 mg and ≤ 15000mg; (3) > 15000 mg and ≤ 30000 mg; (4) > 30000 mg.

The outcomes of interest were incident of adverse events developed after GCs initiation included cardiovascular events (hypertension, atherosclerosis, myocardial infraction, heart failure, dyslipidemia),diabetes, gastrointestinalevents(epigastralgia, ulcer), ophthalmologic events (glaucoma, cataract), osteoporosis, osteoporotic fracture, opportunist infections (viral, bacterial, fungal, parasitic), psychiatricevents (depression, psychosis) and skinevents(skin atrophy, purpura, ecchymosis, hair disorder, cushingoid facies, bruising).

Patients with comorbidities developed before GCs initiation were not noted as adverse events because they would be considered «preexisting conditions».

Statistical analysis

The statistical study was conducted using SPSS software, version 23. Kolmogorov Smirnov test was testing the homogeneity of the variables. Data for patients were presented as means and standard deviation for variables normally distributed, while non-normally distributed data were reported as medians and interquartile ranges. Categorical variables were reported as numbers and percentages. To compare the prevalence of adverse effects between the 4 groups of cumulative GCs doses: (1) ≤7500 mg; (2) > 7500 mg and ≤ 15000mg; (3) > 15000 mg and ≤ 30000 mg; (4) > 30000 mg, we used the chi-square test or Fischer's exact test. p values less than 0.05 were considered statistically significant.

To determine factors significantly associated with GCs cessation, we used univariable followed by multivariable logistic regression analysis. Only characteristics often reported in the literature and those with a p-value <0.20 in the univariable analysis were entered in the multivariable analysis.

Results:-

Table 1:- Characteristics of patients with rheumatoid arthritis.

Characteristics	Value (N=168)
Age (years)[a]	56 [51-61]
Gender[b]	
Female	136 (81)
Male	32 (19)
Rheumatoid arthritis duration (months)[a]	120 [48-177]
DAS 28CRP [a]	2.6 [1.8-3.8]
HAQ [a]	0.30 [0.10-0.87]
Comorbidities prior the GCs use[b]	
Cerebrovascular disease	2 (1.1)
Renal disease	5 (2.9)
Diabetes	7 (4.1)
Current smoking	15 (8.9)
GCs use[b]	
Never use	8 (4.8)
former use	65 (38.7)
Curent use	95 (56.5)
GCs duration[b] (N=160)	
≤6mois	2(1.2)
>6mois	158 (98.7)
Average daily dose of GCs[b] (N=160)	
≤2.5mg	15 (9.4)
2.5mg<≤7.5mg	58 (36.3)
>7.5mg	87 (54.3)
GCs cumulative dose[a] (N=160)	14400 [7000-25200]
GCs cumulative dosescategories[b] (N=160)	
≤ 7500mg	52 (32.5)
7500mg <≤15000mg	30 (18.8)
15000mg <≤30000mg	52 (32.5)
> 30000mg	26 (16.3)
csDMARDcurrent use[b]	155 (92.3)
NSAIDs current use[b]	48 (28.6)
bDMARDcurrentuse[b] (N=84)	
Rituximab	42 (50)
Etanercept	15 (17.8)
Adalimumab	12 (14.2)
Tocilizumab	15 (17.8)
Adverse effects in GCsusers[b] (N=160)	
Cardiovascularevents	51 (31.9)
Diabetes	37 (23.1)
Gastrointestinal events	68 (42.5)
Osteoporosis	37 (23.1)
Osteoporotic Fracture	5 (3.1)
Psychiatric events	9 (5.6)

Ophthalmologic events	30 (18.8)
Opportunist Infections	25 (15.6)
Skin events	113 (71.5)

[a]= medians and interquartile ranges; [b] = numbers and percentages

GCs: glucorticosteroids; csDMARD: conventional synthetic disease modifying anti-rheumatic drug;NSAIDs: non-steroidal anti-inflammatory drugs; bDMARD: biological disease-modifying anti-rheumatic drug

Table 2:- Comparison of prevalences of adverse events between the 4 groups of cumulative glucorticosteroids doses.

	Cumulative GCs doses (mg)				
GCs adverse events	≤7500 N=52	7500< ≤15000 N=30	15000<≤30000 N=52	>30000 N=26	p
Cardiovascularevents[a]	7 (13.7)	13 (25.5)	14(27.5)	17 (33.3)	0.001
Diabetes[a]	6 (16.2)	7 (18.9)	10 (27)	14 (37.8)	0.04
Gastrointestinal events[a]	19 (27.9)	19 (27.9)	20 (29.4)	10 (14.7)	0.08
Osteoporosis[a]	9 (24.3)	8 (21.6)	16 (43.2)	4(10.8)	0.31
Psychiatric events[a]	2 (22.2)		4 (44.4)	3 (33.3)	0.2
Ophtalmologic events[a]	4 (13.3)	7 (23.3)	9 (30)	10 (33.3)	0.02
Opportunist infections [a]	6 (24)	6 (24)	8 (32)	5 (20)	0.6
Skin events[a]	30 (26.5)	22 (19.5)	39 (34.5)	22 (19.5)	0.052

GCs: glucorticosteroids
[a] numbers and percentages

Table 3:- Factors associated with glucorticosteroids cessation.

		Univariable	Analysis	Mutivariable	analysis	
	P	OR	IC 95%	p	OR	IC 95%
Age (female)	0.31	0.98	0.95-1.01			
Gender	0.29	0.64	0.27-1.46			
RA duration	0.059	0.99	0.99-1	0.02	0.8	0.6-0.9
DAS 28 CRP	0.025	1.30	1.03-1.65	0.07	1.29	0.97-1.71
HAQ	0.037	1.87	1.03-3.38	0.15	1.64	0.83-3.25
csDMARD use	0.45	0.62	0.18-2.12			
bDMARD use	0.31	1.38	0.73-2.60	0.13	1.70	0.84-3.44
NSAIDs use	0.75	1.12	0.55-2.28			

csDMARD: conventional synthetic disease modifying anti-rheumatic drug; bDMARD: biological disease-modifying anti-rheumatic drug; NSAIDs: non-steroidal anti-inflammatory drugs

We recruited 168 patients with RAwith a median age of 56 years. The median duration of RA disease was 120 months. 155 patients were treated with conventional disease-modifying anti-rheumatic drug(csDMARD) and 84 with biological disease-modifying anti-rheumatic drug (bDMARD).During the RA duration, a total of 160 patients were prescribed GCs;the majority used high average daily dose (54.3%) for a long period (98.7%). The median of cumulative GCs dose was14400mg. The most common adverse events in GCs users were skin events (71.5%) followed by gastrointestinal (42.5%) and cardiovascular events (31.9%). (Table 1)

The highest prevalences of diabetes,cardiovascular and ophthalmologic events were seen withhighest cumulative GCs doses (>30000mg)compared to other categories of cumulative dosesbelow 30000mg. However, in the case of other adverse events (osteoporosis, gastrointestinal, psychiatric, opportunist infections and skindisorder), the risk did not substantially change between the lowest and the highest cumulative GCs doses categories. (Table 2)

A multivariable regression revealed that increasing RA duration was negatively associated with the GCs cessation in our RA patients (OR 0.8, IC95%: 0.6-0.9). This association was statistically significant (p=0.02). No association was observed with NSAIDs, csDMARD and bDMARD use neither with age, gender nor with RA activity and HAQ scores. (Table 3)

Discussion:-

During RA treatment, GCs are prescribed for a short time to relieve symptoms until disease-modifying anti-rheumatic drugsDMARDs exerts their therapeutic effect or to manage RA flare or DMARDs failure(3,12).However, in some patients, it is stilldifficult to discontinue GCs treatment even after the purpose of their use is achieved(3).

GCs use is a serious concern in RA treatment since it could be associated with many side effects thatmay influence negatively the patient outcomes(11).

In the current study, the prevalence of RA patients currently using GCs was (56.5%) which is consistent with some existing data from other series(4,13).

The majority of our patients used high daily dose of GCs (54.3%) for a long period (98.7%). Many studies(2,14)had noted the chronic prescription of GCs in RA patients and the difficulty to eliminate its. The lack of a consistent definition of ‘‘daily high dose" is a critical barrier in comparing our finding to prior studies (15,16).

Our data showed that GCs users had developed various adverse events. Skin, gastrointestinal and cardiovascular events were the most common side effects with the prevalence of 71.5%, 42.5% and 31.9% respectively. Previous studies haddemonstrated an increased risk of potential adverse effects in GCs users includingcardiovascular, gastrointestinal, diabetes, osteoporosis, opportunist infections, psychiatric, ophthalmologic and skin problems (11,12,15,16).

When considering the impact ofcumulative GCs dose on toxicity, it has been suggested that cumulative dose of 40g is threshold for increasing mortality(2).

Several studies had confirmed the association between the highest cumulative GCs doses and the highest increase in risk development of diabetes, cardiovascular and ophthalmologic events(6,12,17,19).Likewise, our results clearly demonstrated that patients with highestcumulative GCsdoses(>30000mg) experienced higher incidence rates of cardiovascular, diabetes and ophthalmologic events.

Thus, our data supported the concerns about the safety of high cumulative GCs doses use in patients with RA, as well as the conservative approach to GCs use recommended by the 2015 ACR, the 2019 EULAR and the 2019 SFR guidelines to minimize CGs side effects in RA (8_10).

The absence of change between the lowest and the highest cumulative GCs doses categories in the case of osteoporosis, gastrointestinal, psychiatric, opportunist infections and skin disorder might be explained by an increase in risk with short-term, high GCs dose treatment while overall cumulative dose is low(17).

When exploring factors favoring GCs cessation, we found that only RA duration was associated with GCs discontinuation, while the association with bDMARD use did not reach statistically significant threshold. Although this may seem to contradict our knowledge that bDMARD usemay help to promote GCscessation(6,11).

Prior studies had consistently provided a strong association between bDMARD initiation and GCs reducing or eliminating use(5,11).Furthermore, Nilsson et al.(20) had noted that one third of their patients had eliminated GCs after anti-TNF initiation. The absolute decrease or cessation of GCs in patients underbDMARD could be explained by the impact of bDMARD on steroids sparing(5).

Concerning the association between GCs cessation and RA scores, it was discussed in the literature with contradictory results.

Rachel J. Black(6) had showed that patients with higher HAQ scores were more likely to start GCs and less likely to withdraw its. While, RA activity score had no influence on GCs cessation. Neumann et al. (5)had reported that decrease in GCs use occurred as RA activity score improved.

The lack of association between GCs discontinuation and disease activity (DAS28 CRP) or HAQ scores, may encourage clinicians to eliminate GCs use in our RA patients.

In contrast to the results of the current study, previous studies(6,19) hadnoted thatage and gender were consistently associated with GCs cessation. It is reported that older patients and malesare less likely to discontinue GCs treatment.

Some limitations of the present study should be recognized.

First, because patients may take GCs at doses lower or higher than those noted in their files, calculating cumulative doses may be underestimate or overestimate. Additionally, as this was a retrospective observational study, it was impossible to explore the patient background factors that may influenced the adverse events development.

Finally, the number of adverse events was relatively small, which may reduce the power and strength of our conclusion. However, this study produced important findings related to GCs use in RA patients and the effects of cumulative GCs doses on adverse events development.

Conclusion:-

Our study provided evidence that higher cumulativeGCs doses increased risk of experiencing diabetes, cardiovascular and ophthalmologic events and that RA duration was the only predictor of GCs cessation in our RA patients.

When considering the prevalence of our patients prescribed high dose of GCs for a long periodeven with the bDMARD use, it is obvious that existing guidelines(8_10)on the management of GCs in RA patients were still not fully implemented by rheumatologists.

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