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**ORIGINAL ARTICLE****Retrospective Study**

- 53 Blood glucose changes surrounding initiation of tumor-necrosis factor inhibitors and conventional disease-modifying anti-rheumatic drugs in veterans with rheumatoid arthritis

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Retrospective Study

Blood glucose changes surrounding initiation of tumor-necrosis factor inhibitors and conventional disease-modifying anti-rheumatic drugs in veterans with rheumatoid arthritis

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Abstract

AIM

To determine the scope of acute hypoglycemic effects for certain anti-rheumatic medications in a large retrospective observational study.

METHODS

Patients enrolled in the Veterans Affairs Rheumatoid Arthritis (VARA) registry were selected who, during follow-up, initiated treatment with tumor necrosis factor inhibitors (TNFi's, including etanercept, adalimumab, infliximab, golimumab, or certolizumab), prednisone, or conventional disease-modifying anti-rheumatic drugs (DMARDs), and for whom proximate random blood glucose (RBG) measurements were available within a window 2-wk prior to, and 6 mo following, medication initiation. Similar data were obtained for patients with proximate values available for glycosylated hemoglobin A1C values within a window 2 mo preceding, and 12 mo following, medication initiation. RBG and A1C measurements were compared before and after initiation events using paired *t*-tests, and multivariate regression analysis was performed including established comorbidities and demographics.

RESULTS

Two thousands one hundred and eleven patients contributed at least one proximate measurement surrounding the initiation of any examined medication. A significant decrease in RBG was noted surrounding 653 individual hydroxychloroquine-initiation events (-3.68 mg/dL, $P = 0.04$), while an increase was noted for RBG surrounding 665 prednisone-initiation events ($+5.85$ mg/dL, $P < 0.01$). A statistically significant decrease in A1C was noted for sulfasalazine initiation, as measured by 49 individual initiation events (-0.70% , $P < 0.01$). Multivariate regression analyses, using methotrexate as the referent, suggest sulfasalazine ($\beta = -0.58$, $P = 0.01$) and hydroxychloroquine ($\beta = -5.78$, $P = 0.01$) use as predictors of lower post-medication-initiation RBG and A1C values, respectively. Analysis by drug class suggested prednisone (or glucocorticoids) as predictive of higher medication-initiation event RBG among all start events as compared to DMARDs, while this analysis did not show any drug class-level effect for TNFi. A diagnosis of congestive heart failure ($\beta = 4.69$, $P = 0.03$) was predictive for higher post-initiation RBG values among all medication-initiation events.

CONCLUSION

No statistically significant hypoglycemic effects surrounding TNFi initiation were observed in this large cohort. Sulfasalazine and hydroxychloroquine may have epidemiologically significant acute hypoglycemic effects.

Key words: Disease modifying anti-rheumatic drugs; Drug toxicity; Glucocorticoids; Rheumatoid arthritis; Tumor necrosis factor inhibitors

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Core tip: Clinicians should be cognizant of the potential for rare hypoglycemic effects of the conventional disease-modifying anti-rheumatic drugs hydroxychloroquine and sulfasalazine, in addition to the well-known hyperglycemic effects of glucocorticoids. Although case reports describe dramatic sporadic hypoglycemic events with the initiation of tumor necrosis factor inhibitors, these effects were not confirmed in our large retrospective study.

Wood PR, Manning E, Baker JF, England B, Davis L, Cannon GW, Mikuls TR, Caplan L. Blood glucose changes surrounding initiation of tumor-necrosis factor inhibitors and conventional disease-modifying anti-rheumatic drugs in veterans with rheumatoid arthritis. *World J Diabetes* 2018; 9(2): 53-58 Available from: URL: <http://www.wjgnet.com/1948-9358/full/v9/i2/53.htm> DOI: <http://dx.doi.org/10.4239/wjd.v9.i2.53>

INTRODUCTION

Current disease models suggest important links between activation of the innate immune system and obesity, the metabolic syndrome, and diabetes^[1]. In particular, obesity has been associated with activation of the tumor necrosis factor (TNF)-alpha pathway, a cytokine system important in the treatment of many autoimmune diseases.

Tumor necrosis factor TNF inhibitors have revolutionized the care of patients with rheumatoid arthritis (RA), proving highly effective in controlling signs and symptoms of disease, and reducing erosive progression in patients with moderate-to-severe disease. Etanercept, a soluble fusion protein inhibitor of TNF, has an extensive safety record that is generally highly favorable, but sporadic and anecdotal events have been reported indicating potential side effects on glucose homeostasis.

These reports include descriptions of radical and immediate hypoglycemia and improved glucose tolerance with drug initiation among diabetics^[2]. These have occurred in patients with established diagnoses of type II diabetes and psoriasis^[3,4] or psoriatic arthritis^[5]. Events have also occurred in RA patients taking etanercept^[6]. Hypoglycemic episodes have also been observed in non-diabetic patients^[7]. Furthermore, prospective study of obese subjects has shown improved fasting glucose, adiponectin ratios, and other glucose tolerance markers in patients treated prospectively with etanercept^[8].

In addition to anecdotal effects of TNF inhibitors (TNFi) on blood glucose homeostasis, literature exists which suggests hypoglycemic effects for other immunosuppressive medications used in the treatment of RA. These include the conventional disease modifying anti-rheumatic drug (DMARD) sulfasalazine^[9]. Hydroxychloroquine, another DMARD and anti-malarial, has also been noted to have effects on glucose and lipid metabolism beyond its anti-inflammatory role^[10], and prospective studies have shown a decreased risk of incident diabetes among RA patients who use hydroxy-

chloroquine^[11].

Effects on blood glucose and hemoglobin A1C surrounding medication initiation were therefore examined in a cohort of veterans with established RA who initiated treatment on TNFi, prednisone, and DMARDs.

MATERIALS AND METHODS

VARA registry

This retrospective analysis used data obtained from US veterans with RA who were enrolled in the Veterans Affairs Rheumatoid Arthritis (VARA) registry. VARA is an ongoing, longitudinal, multicenter registry that included patients from 12 VA medical centers (Birmingham AL, Brooklyn NY, Dallas TX, Denver CO, Jackson MS, Iowa City IA, Little Rock AR, Omaha NE, Portland OR, Philadelphia PA, Salt Lake City UT, and Washington, DC, United States). The study was approved by local IRBs (Colorado Multiple Institutional Review Board #06-0956) and the Scientific and Ethical Advisory Board of the VARA registry for analysis of VARA and VA administrative data; all patients provided written consent prior to enrollment in the VARA registry.

Patients

All patients reported disease onset after 18 years of age and fulfilled the 1987 American College of Rheumatology (ACR) classification criteria for RA^[12]. Registry members were selected for analysis if they began DMARD, prednisone, or TNFi therapy for the first time between the periods of March 2003 (the first date after which multiple TNFi agents were available within VA) and December 2014. Initial therapy with any of the following agents qualified a subject for inclusion: etanercept, adalimumab, infliximab, golimumab, certolizumab, methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, or prednisone. Patients with or without established diagnoses of diabetes were included for analysis.

Data sources

In addition to VARA registry data, administrative VA databases were utilized in the analysis, including the Corporate Data Warehouse (CDW), National Pharmacy Extract, and Pharmacy Benefits Management (PBM) database^[13]. Descriptions of these databases in the context of this registry have been published elsewhere^[14].

Statistical analysis

The primary outcomes in this study were the differences in RBG and A1C between measurements prior to, and subsequent to, medication exposure. Pre-exposure RBG and A1C values were selected as the most proximal preceding value available before medication initiation within a 6 mo window. For RBG, post-exposure values were selected as a most proximal value post-initiation within a 2 wk to 6 mo window. For A1C, post-values were selected as the most proximal value post-initiation within a 2- to 12- mo window.

Paired *T*-tests were performed comparing pre- and post- values, with an alpha of 0.05 set as a significance threshold. Baseline demographic characteristics were obtained, as well as baseline characteristics for validated comorbidities^[15]: Age, sex, diabetes diagnosis, cancer diagnosis, chronic kidney disease, chronic lung disease, and congestive heart failure. Finally, multivariate linear regression analysis was performed, examining specific agent and medication class initiated, age, sex, and comorbidities as predictors for change in blood glucose and A1C at the time of medication initiation. Statistical analysis was performed using Stata v. 11.2 (College Station TX).

RESULTS

Baseline characteristics

A total of 2111 patients contributed 4,028 medication-initiation events with glucose measurements available for analysis. Individual patients could contribute more than one initiation event for analysis when applicable, but only one, first-start, event was included per medication-patient pairing. The mean age of examined patients was 63.9 years, and 90% were male, reflecting demographics of the Veterans Affairs health care system patient population at-large, which is disproportionately male and middle-aged. Large numbers were initiated on methotrexate, etanercept, sulfasalazine, leflunomide, hydroxychloroquine, adalimumab, and prednisone during follow-up. Initiation of certolizumab and golimumab were far less represented in these data.

Change in A1C and RBG

Paired *t*-tests (Table 1) revealed significant RBG decreases in 653 initiation-events of hydroxychloroquine (-3.68 mg/dL, $P = 0.04$), and higher RBG values following 665 prednisone-initiation events (+5.85 mg/dL, $P < 0.01$). A1c values were significantly lower following 49 sulfasalazine starts (-0.70%, $P < 0.01$).

A larger, unpaired analysis of all available pre- and post- initiation glucose values surrounding drug initiation events confirmed lower post-A1C values following sulfasalazine initiation and higher RBG values following prednisone. In addition, a trend towards lower RBG values following sulfasalazine initiation was seen (-2.73 mg/dL, $P = 0.09$). In addition, a trend was seen towards lower A1C values following initiation of etanercept (-0.30%, $P = 0.10$) and higher A1C values following certolizumab initiation (0.48%, $P = 0.09$).

Multivariate linear regression analyses

In multivariate analyses that accounted for comorbidities and demographic characteristics, we evaluated the effect of individual DMARDs and TNFi's on individual changes in A1C and RBG using methotrexate as the referent. In these analyses, hydroxychloroquine initiation predicted a decrease in RBG (Table 2) compared to methotrexate initiation when accounting for other variables (coefficient

Table 1 Changes in paired A1C and random blood glucose surrounding medication-initiation events

Medication	<i>n</i>	Difference (mg/dL or % glycosylation)	Confidence interval		<i>P</i> value
Random blood glucose					
Etanercept	311	-0.06	-4.91	4.79	0.98
Adalimumab	302	1.03	-3.41	5.46	0.65
Certolizumab	5	-5.20	-26.60	16.19	0.54
Golimumab	13	-17.61	-37.54	2.31	0.08
Infliximab	147	-1.90	-9.45	5.65	0.62
Methotrexate	831	2.08	-7.48	4.90	0.15
Leflunomide	290	-0.48	-6.84	5.88	0.88
Hydroxychloroquine	653	-3.68	-7.15	0.20	0.04
Sulfasalazine	335	-0.38	-4.92	4.17	0.87
Prednisone	665	5.85	2.20	9.51	< 0.01
Hemoglobin A1C					
Etanercept	35	-0.17	-0.50	0.17	0.33
Adalimumab	43	0.04	-0.34	0.42	0.83
Certolizumab	1	0.20	n/a	n/a	n/a
Golimumab	4	-0.65	-3.47	2.17	0.52
Infliximab	20	-0.36	-0.95	0.23	0.22
Methotrexate	107	-0.11	-0.35	0.14	0.40
Leflunomide	51	-0.02	-0.40	0.35	0.91
Hydroxychloroquine	98	-0.15	-0.40	0.11	0.25
Sulfasalazine	49	-0.70	-1.08	0.31	< 0.01
Prednisone	68	-0.01	-0.25	0.24	0.96

n/a: Insufficient numbers to calculate.

Table 2 Multivariate regression analysis of glucose changes surrounding medication-initiation events

Predictor variable	Hemoglobin A1C				Random blood glucose			
	Coefficient	Confidence interval		<i>P</i> value	Coefficient	Confidence interval		<i>P</i> value
Sex	-0.12	-0.60	0.36	0.63	1.75	-3.80	7.30	0.54
Age	0.00	-0.01	0.02	0.71	0.00	-0.16	0.15	0.98
Diabetes	0.10	-0.20	0.40	0.50	0.02	-3.33	3.36	0.99
Malignancy	-0.20	-0.50	0.09	0.17	0.54	-3.31	4.39	0.78
Coronary artery disease	0.07	-0.30	0.43	0.72	-1.48	-6.54	3.58	0.57
Congestive heart failure	-0.07	-0.37	0.22	0.62	4.69	0.45	8.92	0.03
Chronic lung disease	0.14	-0.11	0.38	0.27	-0.95	-4.16	2.27	0.56
Chronic kidney disease	-0.35	-0.78	0.07	0.11	-5.57	-12.67	1.52	0.12
Hypertension	0.01	-0.35	0.38	0.95	-0.81	-4.50	2.88	0.67
Medication (comparator is methotrexate)								
Adalimumab	0.17	-0.28	0.62	0.46	-0.87	-6.83	5.09	0.78
Golimumab	-0.56	-1.81	0.70	0.39	-19.88	-44.57	4.82	0.12
Certolizumab	0.41	-2.06	2.87	0.75	-7.02	-46.55	32.51	0.73
Infliximab	-0.30	-0.90	0.30	0.32	-3.85	-11.76	4.06	0.34
Etanercept	-0.08	-0.56	0.40	0.75	-2.07	-7.97	3.84	0.49
Leflunomide	0.05	-0.37	0.47	0.81	-2.66	-8.68	3.36	0.39
Hydroxychloroquine	-0.01	-0.36	0.33	0.94	-5.78	-10.38	-1.17	0.01
Sulfasalazine	-0.58	-1.00	-0.16	0.01	-2.56	-8.26	3.15	0.38
Prednisone	0.11	-0.26	0.49	0.55	3.76	-0.82	8.34	0.11
Medication class (comparator is conventional DMARDs)								
TNFi	0.06	-0.23	0.35	0.68	0.30	-3.47	4.07	0.88
Glucocorticoid	0.20	-0.13	0.53	0.23	6.32	2.40	10.24	< 0.01

DMARDs: Disease-modifying anti-rheumatic drugs.

= -5.77, CI = -10.4- -1.2, *P* = 0.01). Additionally, sulfasalazine initiation predicted decreased A1C values compared to methotrexate-initiators (β = -0.58, *P* = 0.01). Of the various comorbidities examined, only congestive heart failure (ever) was found to predict changes in RBG surrounding medication initiation (β = 4.57, *P* = 0.03). A separate regression analysis by

medication class rather than individual agent revealed corticosteroid (prednisone) use as a predictor for positive change in RBG as compared to DMARD initiators as the referent (β = 6.32, *P* < 0.01); medications as analyzed by class did not, however, predict A1C change, and CHF was the only demographic or comorbidity predictor for higher RBG.

DISCUSSION

Our data are unable to firmly demonstrate an effect on blood glucose for etanercept or other TNFi in a cohort of rheumatoid arthritis patients, although trends in these data are somewhat supportive of hypoglycemic effects previously suggested in case reports and series for etanercept, in particular. As these events are rare, risk factors and biologic processes underlying TNF-associated hypoglycemic events might be better clarified through the use of case-control studies comparing specific patients with these events with selected controls. In addition, a similar investigation of glycemic effects of both DMARD and TNFi in spondyloarthritis patients is warranted, as soon as adequate registry data are available in these diseases.

The detection of blood glucose increases following the initiation of prednisone—a well-established phenomenon and pharmacologic effect—lends internal validity to our study. Utilizing the described techniques, modest but statistically significant medication-initiation effects towards lower blood glucose also appear to be present for sulfasalazine and hydroxychloroquine.

The strong signal for lower A1C following sulfasalazine initiation (but not in RBG) may be consistent with the latency of action for some traditional DMARDs, which may also include their hypoglycemic effects. The lack of predictive value for change in glucose when these data are analyzed by drug class (other than glucocorticoids) also suggest that at least some of these effects are medication-specific. These may be separate from, or in addition to, global anti-inflammatory effects on glucose tolerance. These effects may combine with favorable effects for these agents on lipid profiles^[16] and to partially explain the previously described cardioprotective profile of hydroxychloroquine. The effects of sulfasalazine and hydroxychloroquine seen in our cohort may also support further investigation of these medications as therapeutic hypoglycemic agents.

It is notable that a diagnosis of diabetes did not strongly influence change in glucose values relative to DMARD medications by our regression analyses. This result suggests that hypoglycemic effects for hydroxychloroquine and sulfasalazine are possibly independent of an insulin-resistant state.

Limitations of our study include the wide variation in RBG values at any given time. In addition, we did not investigate effects of glucocorticoids besides prednisone, nor non-TNFi biologic agents, as we did not expect adequate data for analysis in this registry for these agents. Our results may be confounded by variations in body mass index and other unmeasured patient characteristics using these data sources. These include our failure to include disease activity measures, which may be only partially accounted for by our inclusion of prednisone as a surrogate for disease activity and severity. Finally, as with other VARA publications, our data are somewhat limited by the atypical demographics of the Veterans Affairs population (dis-

proportionately male) relative to the general population with RA, and it is theoretically possible that these results could be somewhat different in a younger, more female population.

Clinicians should be cognizant of the potential for rare hypoglycemic effects of the conventional DMARDs hydroxychloroquine and sulfasalazine, in addition to the well-known hyperglycemic effects of prednisone.

ARTICLE HIGHLIGHTS

Research background

Several case reports and series have described dramatic acute hypoglycemic effects for the immunosuppressive agents collectively called tumor necrosis factor inhibitors (TNFi's). In addition, studies have shown various cardioprotective and metabolic effects for conventional anti-rheumatic therapies; however, few studies have examined acute blood glucose effects for these agents in large population studies.

Research motivation

A better estimate of frequency and scale hypoglycemia associated with the initiation of medicines for users of TNFi and other anti-inflammatory medications may give insight into the role of cytokines and the inflammatory cascade in glucose tolerance as well as better estimate risks and benefits for these medications to the clinician.

Research objectives

We wished to determine whether initiation of tumor necrosis factor inhibitors in rheumatoid arthritis patients leads to reductions in blood glucose as measured by random blood glucose or glycosylated hemoglobin A1c. Simultaneously, we wished to investigate for similar effects in conventional antirheumatic drugs, given the established lipid homeostasis and cardioprotective effects for these agents.

Research methods

An observational registry linking pharmacy, clinical laboratory, and other data was utilized to retrospectively identify the time of prescription of the agents in question. This registry and linked data was used to retrospectively identify glucose measures proximate to these medication start events, so that changes in blood glucose surrounding the medication start could be inferred.

Research results

Cohort-level glucose effects were not identified in this registry surrounding the start of tumor-necrosis factor inhibitors, although glucose-lowering changes were identified surrounding the initiation of the conventional antirheumatic treatments sulfasalazine and hydroxychloroquine. Hyperglycemic changes surrounding prednisone were identified, lending further internal validity to these results.

Research conclusions

This study adds to the literature supporting the potentially beneficial metabolic effects of conventional anti-rheumatic therapies sulfasalazine and hydroxychloroquine beyond their general anti-inflammatory effects. These data also lend reassurance against large-scale prevalence for previously reported adverse hypoglycemic effects for tumor-necrosis factor inhibitors. The results point to the need for additional, similar studies in other populations, particularly those with spondyloarthritis syndromes such as psoriatic arthritis.

Research perspectives

This study, while a null result regarding tumor necrosis factor-inhibitor-associated hypoglycemic effects, points to the need for additional clarification on the physiology and causes for hypoglycemic events with these medications. We suggest the need for similar studies in psoriasis and psoriatic arthritis patients, as well as the potential utility of a case-control approach for the future study of dramatic hypoglycemic effects and events

with immunosuppressive medications.

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