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ORIGINAL ARTICLE

Population-level interest in anti-rheumatic drugs in the COVID-19 era: insights from Google Trends

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Abstract

Introduction/objective The general public may utilize online information through search engines for implications and risks of some anti-rheumatic drugs. These drugs have been used in the management of coronavirus disease 2019 (COVID-19) and associated inflammatory sequelae or cytokine storm of infection. Therefore, the objective of this study was to investigate the population-level interest in anti-rheumatic drugs during the COVID-19 era, by analyzing changes in Google search frequency data.

Method To obtain the relative search volume (RSV) of anti-rheumatic drugs, we queried Google Trends for 78 search terms representing non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, antigout agents, conventional disease-modifying anti-rheumatic drugs (DMARDs), immunosuppressants, biologics, and Janus kinase (JAK) inhibitors within the USA. Three 8-week periods in 2020 (March 15–May 9), (May 10–July 4), and (July 5–August 29) representing the initial- and short-term periods were compared to overlapping periods of the preceding 3 years (2017–2019).

Results We found statistically significant increases in RSV for colchicine, hydroxychloroquine, tocilizumab (and its brand name-Actemra), and anakinra, and statistically significant decreases among brand names of immunosuppressive agents (i.e., mycophenolate mofetil, azathioprine, cyclophosphamide, tacrolimus, cyclosporine) during both the initial- and short-term COVID-19 periods as compared to overlapping periods of the preceding 3 years.

Conclusion There were significant increases in RSV of colchicine, hydroxychloroquine, tocilizumab, and anakinra during both initial- and short-term COVID-19 periods when compared to overlapping periods of the preceding 3 years reflecting a heightened level of information-seeking on these drugs during the pandemic. Rheumatologists should address this increase in informational demand. Further research assessing medium- and long-term interest in anti-rheumatic drugs is required to increase our knowledge on this new pandemic.

Key Points

- *This study was aimed to investigate the population-level interest in anti-rheumatic drugs in the COVID-19 era, by analyzing changes in Google search frequency data.*
- *Significant increases were seen in relative searches for colchicine, hydroxychloroquine, tocilizumab, and anakinra during both initial and short-term COVID-19 periods when compared to similar periods of 2017–2019 reflecting a heightened level of information-seeking on these drugs during the pandemic.*
- *Rheumatologists should address this increase in informational demand for colchicine, hydroxychloroquine, tocilizumab, and anakinra.*

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Keywords Anakinra · Colchicine · Google search · Hydroxychloroquine · Internet · Tocilizumab

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that emerged from Wuhan China in December 2019, causing the disease that is referred to as coronavirus disease 2019 (COVID-19). This disease spread rapidly throughout China and other regions of the world, resulting in the World Health Organization (WHO) declaring COVID-19 a pandemic [1]. Globally, a total of 28,329,790 confirmed cases of COVID-19, including 911,877 deaths, had been reported to the WHO, as of September 12, 2020. The country with the highest number of cases and deaths is the USA, with 6,341,309 confirmed cases and 190,787 deaths [2].

Patients taking anti-rheumatic drugs share concerns regarding a potential increased risk of contracting COVID-19 infection [3–8], and the public may have searched online information for the implications and risks of some anti-rheumatic drugs, which have been used in the management of COVID-19 infection and associated inflammatory sequelae or cytokine storm [9–15]. Therefore, population-level interest in anti-rheumatic drugs in the COVID-19 era should be investigated to increase our understanding of this new pandemic.

During the past decade, an increasing number of scientific studies have documented the importance of Google Trends in the detection of an epidemic and monitoring public interest [16–20]. It has been used to study previous epidemics such as influenza [21, 22], Dengue fever [23], and Zika virus [24]. In light of COVID-19, Google Trends data has been used to investigate population-level interest in several treatment approaches including urologic procedures [25], hip and knee arthroplasties [26], facial plastic surgery [27], and cosmetic procedures [28]. Furthermore, an interesting study investigating Google searches of hydroxychloroquine is available in the literature [29]. Our study would expand the knowledge on Google searches of anti-rheumatic drugs beyond hydroxychloroquine.

Therefore, we aimed to investigate the population-level interest in anti-rheumatic drugs in the COVID-19 era, by analyzing changes in Google search frequency data.

Materials and method

Google Trends presents the frequency of Google search terms in a normalized form as a relative search volume (RSV). Values of RSV range between 0 and 100, where 100 represents to the peak popularity for the search term [30]. The information on Google Trends and its data are presented in detail in the literature [17, 18].

We selected search terms that encompass anti-rheumatic drugs including non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, antigout agents, conventional Disease-modifying anti-rheumatic drugs (DMARDs), immunosuppressant agents, interleukin (IL)-6 inhibitors, IL-1 inhibitors, tumor necrosis factor (TNF) inhibitors, IL-17 inhibitors, IL-12/23 pathway targeting agents, T cell co-stimulation modulators, B cell-targeting agents, Janus kinase (JAK) inhibitors, and phosphodiesterase-4 (PDE4) inhibitor. Both generic and brand names of the drugs were included, and brand names were obtained from UpToDate [31]. We used a total of 78 search terms as the following: NSAIDs, Ibuprofen, Advil, Indomethacin, Indocin, Diclofenac, Voltaren, Naproxen, Aleve, Meloxicam, Mobic, Glucocorticoids, Prednisone, Deltasone, Colchicine, Colcrys + Mitigare, Allopurinol, Zyloprim, Febuxostat, Uloric, Hydroxychloroquine, Plaquenil, Methotrexate, Otrexup + Rasuvo + Rheumatrex + Trexall, Sulfasalazine, Azulfidine, Leflunomide, Arava, Mycophenolate mofetil, CellCept, Azathioprine, Imuran, Cyclophosphamide, Cytoxan, Tacrolimus, Prograf, Cyclosporine, Gengraf + Neoral + Sandimmune, Tocilizumab, Actemra, Sarilumab, Kevzara, Anakinra, Kineret, Canakinumab, Ilaris, Rilonacept, Arcalyst, Etanercept, Enbrel, Infliximab, Remicade, Adalimumab, Humira, Certolizumab, Cimzia, Golimumab, Simponi, Secukinumab, Cosentyx, Ixekizumab, Taltz, Ustekinumab, Stelara, Guselkumab, Tremfya, Abatacept, Orencia, Rituximab, Rituxan, Belimumab, Benlysta, Tofacitinib, Xeljanz, Baricitinib, Olumiant, Apremilast, and Otezla. To obtain the relative frequency of these selected search terms, we queried Google Trends with the selection of "United States," "01/01/2017–09/09/2020," and "Web Search" settings on September 9, 2020. We imposed no category restrictions when querying Google Trends and exported the Google Trends weekly RSV data for further analysis.

Search term RSV during the initial 8-week period (March 15–May 9, 2020), after US President Donald Trump declared a national emergency due to the COVID-19 outbreak, was compared with overlapping periods of the preceding 3 years (2017–2019) to investigate initial stage interest in the drugs. In addition, we compared May 10–July 4, 2020, and July 5–August 29, 2020, periods with overlapping periods in 2017–2019 to investigate short-term interest. Previous studies included the years of 2015 and 2016 as well [25, 26]; however, to avoid selection bias in our study, we excluded data from the years 2015 and 2016 because some anti-rheumatic drugs were less popular treatments during that time.

To investigate whether RSV had changed between the periods, we performed generalized estimating equations using a model of gamma with log link. The analysis was conducted using SPSS version 21.0, IBM. The level of significance was established at the 0.05 level.

Results

During the initial period, March 15–May 9, 2020, the RSV of NSAIDs (% change: + 88.4%; $p = 0.030$), diclofenac (+ 7.7%; $p = 0.018$), colchicine (+ 24.4%; $p < 0.001$), febuxostat (+ 101.3%; $p < 0.001$), hydroxychloroquine (+ 3613.0%; $p < 0.001$), Plaquenil (+ 635.0%; $p = 0.003$), tacrolimus (+ 12.6, $p = 0.030$), tocilizumab (+ 1253.5%; $p < 0.001$), Actemra (+ 443.6%; $p < 0.001$), sarilumab (+ 442.5%; $p < 0.001$), Kevzara (+ 272.2%; $p < 0.001$), anakinra (+ 188.6%; $p < 0.001$), infliximab (+ 19.2%; $p = 0.005$), Stelara (+ 13.8%; $p = 0.015$), and baricitinib (+ 91.9%; $p = 0.027$) showed a statistically significant increase; conversely, the RSV of Indocin (− 39.4%; $p < 0.001$), Voltaren (− 26.2%; $p < 0.001$), meloxicam (− 6.5%; $p = 0.012$), Mobic (− 38.9%; $p < 0.001$), allopurinol (− 12.6%; $p = 0.006$), Zyloprim (− 27.6%; $p = 0.034$), Uloric (− 39.9%; $p < 0.001$), methotrexate (− 12.6%; $p < 0.001$), Arava (− 29.3%; $p < 0.001$), CellCept (− 15.4%; $p = 0.003$), Imuran (− 31.5%; $p < 0.001$), Cytoxan (− 24.5%; $p < 0.001$), Prograf (− 31.1%; $p < 0.001$), Gengraf + Neoral + Sandimmune (− 28.0%; $p = 0.026$), canakinumab (− 1.3%; $p = 0.046$), Ilaris (− 32.5%; $p = 0.029$), rilonacept (− 14.2%; $p = 0.023$), Remicade (− 12.0%; $p = 0.031$), golimumab (− 37.2%; $p = 0.005$), ixekizumab (− 32.7%; $p = 0.008$), Taltz (− 30.7%; $p < 0.001$), and Rituxan (− 34.4%; $p < 0.001$) displayed a statistically significant decrease as compared to overlapping periods of the preceding 3 years (Table 1).

During the May 10–July 4, 2020, period, Diclofenac (+ 14.8%; $p < 0.001$), Voltaren (+ 222.8%; $p < 0.001$), Febuxostat (+ 72.3%; $p < 0.001$), Hydroxychloroquine (+ 1375.0%; $p = 0.017$), Sulfasalazine (+ 20.0%; $p = 0.010$), Azathioprine (+ 11.6%; $p = 0.055$), Tocilizumab (+ 434.4%; $p < 0.001$), Actemra (+ 87.1%; $p < 0.001$), Anakinra (+ 91.0%; $p < 0.001$), Arcalyst (+ 36.7%; $p = 0.049$), Baricitinib (+ 153.2%; $p < 0.001$), and Olumiant (+ 42.8%; $p = 0.039$) showed a statistically significant increase; conversely, Advil (− 8.6%; $p < 0.001$), Indomethacin (− 10%; $p = 0.023$), Indocin (− 21.7%; $p = 0.006$), Naproxen (− 8.3%; $p < 0.001$), Aleve (− 11.8%; $p < 0.001$), Mobic (− 26.3%; $p < 0.001$), Prednisone (− 7.2%; $p = 0.018$), Methotrexate (− 6.6%; $p = 0.071$), Sulfasalazine (+ 20.0%; $p = 0.010$), Arava (− 20.6%; $p = 0.010$), CellCept (− 21.9%; $p < 0.001$), Imuran (− 22.5%; $p < 0.001$), Cytoxan (− 20.4%; $p < 0.001$), Gengraf + Neoral + Sandimmune (− 29.1%; $p < 0.001$), Etanercept (− 24.7%; $p = 0.029$), Enbrel (− 24.8%; $p = 0.004$), Remicade (− 24.6%; $p < 0.001$), Humira (− 15.4%; $p = 0.002$), Golimumab (− 40.0%; $p = 0.002$), Simponi (− 12.3%; $p = 0.042$), Taltz (− 21.6%; $p = 0.004$), Rituxan (− 25.0%; $p < 0.001$), and Tofacitinib (− 22.0%; $p = 0.012$) displayed a statistically significant decrease compared to preceding 3 years (Table 1).

During the July 5–August 29, 2020, period, Ibuprofen (+ 6.7%; $p = 0.015$), Advil (+ 3.4%; $p = 0.036$, Diclofenac (+ 11.6%; $p < 0.001$), Voltaren (+ 118.8%; $p < 0.001$), Glucocorticoids (+ 22.3%; $p = 0.021$), Colchicine (+ 17.1%; $p < 0.001$), Febuxostat (+ 63.3%; $p < 0.001$), Hydroxychloroquine (+ 2125.0%; $p = 0.046$), Tacrolimus (+ 18.2%; $p = 0.005$), Tocilizumab (+ 400.0%; $p < 0.001$), Actemra (+ 61.5%; $p < 0.001$), Anakinra (+ 71.2%; $p < 0.001$), Infliximab (+ 32.6%; $p < 0.001$), Tremfya (+ 24.0%; $p = 0.017$), and Baricitinib (+ 88.2%; $p < 0.001$) showed a statistically significant increase; conversely, Indocin (− 26.0%; $p < 0.001$), Naproxen (− 8.5%; $p < 0.001$), Aleve (− 7.7%; $p = 0.004$), Mobic (− 20.6%; $p < 0.001$), Uloric (− 45.3%; $p < 0.001$), CellCept (− 13.2%; $p = 0.023$), Imuran (− 19.2%; $p = 0.003$, Cytoxan (− 21.5%; $p = 0.005$), Cyclosporine (− 7.8%; $p = 0.021$), Gengraf + Neoral + Sandimmune (− 29.9%; $p = 0.018$), Arcalyst (− 43.4%; $p < 0.001$), Enbrel (− 19.6%; $p < 0.001$), Remicade (− 19.0%; $p < 0.001$), Humira (− 11.0%; $p = 0.010$), Certolizumab (− 27.8%; $p = 0.027$), Secukinumab (− 27.7%; $p = 0.039$), Cosentyx (− 14.2%; $p = 0.011$), Ixekizumab (− 29.6%; $p = 0.005$), Rituxan (− 22.1%; $p < 0.001$), and Tofacitinib (− 26.8%; $p = 0.012$) displayed a statistically significant decrease compared to preceding 3 years (Table 1).

Discussion

We found statistically significant increases in RSV for colchicine, hydroxychloroquine, tocilizumab (and its brand name-Actemra), and anakinra, and statistically significant decreases among brand names of immunosuppressive agents (i.e., mycophenolate mofetil, azathioprine, cyclophosphamide, tacrolimus, and cyclosporine) during both the initial- and short-term COVID-19 periods as compared to overlapping periods of the preceding 3 years.

In a previous study investigating Google searches indicative of increased purchases of chloroquine and hydroxychloroquine, Liu et al. showed that demand for chloroquine and hydroxychloroquine increased following endorsements by Elon Musk and President Donald Trump [29]. In our study, we detected a statistically significant increase in RSV of hydroxychloroquine in all three periods investigated, indicating continued interest in hydroxychloroquine by the general public.

Aside from hydroxychloroquine, we showed an increased interest in colchicine, tocilizumab, and anakinra in both initial and short terms of COVID-19. The increased public interest in

Table 1 Relative search volume (RSV) of anti-rheumatic drugs

	March 15–May 9				May 10–July 4				July 5–August 29			
	2020	2017–2019	% change	*p* value	2020	2017–2019	% change	*p* value	2020	2017–2019	% change	*p* value
NSAIDs	48.8 ± 10.5	25.9 ± 0.5	+ 88.4	0.030	22.9 ± 0.6	23.1 ± 0.5	− 1.1	0.754	24.1 ± 0.6	23.9 ± 0.6	+ 0.9	0.809
Ibuprofen	49.1 ± 10.6	28.4 ± 0.5	+ 72.9	0.051	28.1 ± 0.6	27.4 ± 0.4	+ 2.6	0.315	29.9 ± 0.6	28.0 ± 0.4	+ 6.7	0.015
Advil	42.3 ± 9.0	29.0 ± 0.3	+ 45.9	0.138	25.8 ± 0.6	28.2 ± 0.4	− 8.6	< 0.001	28.9 ± 0.3	27.9 ± 0.3	+ 3.4	0.036
Indomethacin	74.0 ± 3.0	80.1 ± 1.4	− 7.6	0.067	71.7 ± 2.8	79.8 ± 2.1	− 10.0	0.023	75.5 ± 2.4	79.6 ± 1.4	− 5.1	0.136
Indocin	40.6 ± 3.7	67.1 ± 2.6	− 39.4	< 0.001	46.3 ± 3.5	59.0 ± 3.1	− 21.7	0.006	44.9 ± 2.7	60.6 ± 3.1	− 26.0	< 0.001
Diclofenac	79.5 ± 1.1	73.8 ± 2.1	+ 7.7	0.018	89.1 ± 1.3	77.6 ± 1.8	+ 14.8	< 0.001	90.6 ± 0.8	81.2 ± 1.8	+ 11.6	< 0.001
Voltaren	14.9 ± 0.6	20.2 ± 0.4	− 26.2	< 0.001	67.3 ± 9.2	20.8 ± 0.4	+ 222.8	< 0.001	47.5 ± 2.4	21.7 ± 0.3	+ 118.8	< 0.001
Naproxen	80.5 ± 3.7	81.2 ± 0.9	− 0.8	0.862	74.1 ± 1.3	80.8 ± 0.5	− 8.3	< 0.001	75.4 ± 1.0	82.4 ± 0.8	− 8.5	< 0.001
Aleve	60.9 ± 7.1	53.3 ± 0.4	+ 14.3	0.283	46.9 ± 1.3	53.2 ± 0.6	− 11.8	< 0.001	49.6 ± 1.2	53.8 ± 0.7	− 7.7	0.004
Meloxicam	78.5 ± 1.7	84.0 ± 1.4	− 6.5	0.012	85.6 ± 2.2	85.4 ± 1.5	+ 0.2	0.937	88.5 ± 0.8	89.0 ± 1.2	− 0.5	0.755
Mobic	46.8 ± 1.7	76.5 ± 1.2	− 38.9	< 0.001	55.7 ± 2.1	75.7 ± 1.1	− 26.3	< 0.001	60.8 ± 1.7	76.5 ± 1.7	− 20.6	< 0.001
Glucocorticoids	63.4 ± 6.3	55.5 ± 1.9	+ 14.3	0.227	42.5 ± 2.7	39.2 ± 1.8	+ 8.4	0.309	38.9 ± 2.5	31.8 ± 1.8	+ 22.3	0.021
Prednisone	74.3 ± 2.3	78.0 ± 1.2	− 4.9	0.142	73.1 ± 2.0	78.8 ± 1.3	− 7.2	0.018	76.9 ± 1.1	77.7 ± 1.0	− 1.0	0.609
Deltasone	36.4 ± 4.2	43.5 ± 2.7	− 16.5	0.155	38.8 ± 4.3	42.1 ± 3.1	− 8.0	0.528	39.1 ± 4.0	38.7 ± 3.0	+ 1.1	0.934
Colchicine	66.1 ± 3.4	53.2 ± 1.4	+ 24.4	< 0.001	57.3 ± 2.9	55.2 ± 2.1	+ 3.7	0.572	65.0 ± 1.4	55.5 ± 1.3	+ 17.1	< 0.001
Colcrys + Mitigare	59.9 ± 3.6	65.6 ± 2.9	− 8.7	0.218	62.0 ± 3.2	61.3 ± 2.7	+ 1.1	0.874	63.5 ± 4.1	63.7 ± 1.9	− 0.3	0.971
Allopurinol	68.0 ± 2.6	77.8 ± 2.4	− 12.6	0.006	75.9 ± 2.0	74.8 ± 1.8	+ 1.4	0.703	81.0 ± 2.1	81.2 ± 1.8	− 0.3	0.939
Zyloprim	35.3 ± 5.5	48.7 ± 3.1	− 27.6	0.034	41.4 ± 5.0	45.5 ± 2.9	− 9.1	0.474	41.9 ± 4.9	42.3 ± 2.8	− 0.9	0.947
Febuxostat	62.5 ± 3.5	31.0 ± 2.8	+ 101.3	< 0.001	58.9 ± 1.5	34.2 ± 2.4	+ 72.3	< 0.001	65.9 ± 5.7	40.3 ± 4.5	+ 63.3	< 0.001
Uloric	37.8 ± 2.9	62.8 ± 2.9	− 39.9	< 0.001	34.5 ± 2.4	68.7 ± 2.6	− 49.8	< 0.001	35.0 ± 1.7	64.0 ± 2.4	− 45.3	< 0.001
Hydroxychloroquine	37.1 ± 7.6	1.0 ± 0.0	+ 3613.0	< 0.001	14.8 ± 5.7	1.0 ± 0.0	+ 1375.0	0.017	22.3 ± 10.6	1.0 ± 0.0	+ 2125.0	0.046
Plaquenil	39.5 ± 11.5	5.4 ± 0.2	+ 635.0	0.003	6.8 ± 1.1	5.8 ± 0.1	+ 15.7	0.420	7.4 ± 1.1	5.8 ± 0.2	+ 26.4	0.166
Methotrexate	69.5 ± 2.6	79.5 ± 1.5	− 12.6	0.001	70.0 ± 2.0	75.0 ± 1.9	− 6.6	0.071	73.3 ± 2.2	76.8 ± 1.0	− 4.6	0.142
Otrexup + Rasuvo + Rheumatrex + Trexall	46.0 ± 6.7	49.4 ± 4.0	− 6.9	0.662	53.4 ± 3.4	49.5 ± 3.8	+ 7.8	0.446	53.4 ± 3.9	56.0 ± 4.0	− 4.6	0.645
Sulfasalazine	67.6 ± 1.9	62.1 ± 2.1	+ 8.9	0.051	73.6 ± 4.4	61.4 ± 1.7	+ 20.0	0.010	71.4 ± 4.4	69.2 ± 2.2	+ 3.2	0.657
Azulfidine	34.0 ± 4.8	39.8 ± 2.9	− 14.6	0.302	25.8 ± 4.3	34.9 ± 2.5	− 26.1	0.066	27.0 ± 3.4	33.1 ± 3.2	− 18.4	0.189
Leflunomide	58.0 ± 2.9	55.9 ± 2.8	+ 3.8	0.598	58.3 ± 3.6	55.1 ± 3.0	+ 5.7	0.499	65.5 ± 3.8	61.8 ± 2.9	+ 5.9	0.445
Arava	22.9 ± 1.3	32.3 ± 1.3	− 29.3	< 0.001	26.6 ± 2.3	33.5 ± 1.4	− 20.6	0.010	31.9 ± 2.2	33.8 ± 1.7	− 5.6	0.505
Mycophenolate mofetil	41.8 ± 6.1	42.2 ± 4.3	− 1.1	0.951	47.4 ± 5.1	44.6 ± 4.1	+ 6.2	0.672	51.4 ± 3.8	44.8 ± 3.9	+ 14.6	0.235
CellCept	53.6 ± 2.7	63.4 ± 2.0	− 15.4	0.003	52.4 ± 3.2	67.1 ± 2.3	− 21.9	< 0.001	57.3 ± 2.8	65.9 ± 2.6	− 13.2	0.023
Azathioprine	51.4 ± 7.2	39.0 ± 1.6	+ 31.9	0.090	42.1 ± 1.8	37.8 ± 1.4	+ 11.6	0.055	43.3 ± 2.0	41.0 ± 1.6	+ 5.5	0.375
Imuran	45.5 ± 5.5	66.5 ± 2.1	− 31.5	< 0.001	48.3 ± 3.3	62.3 ± 2.3	− 22.5	< 0.001	53.0 ± 3.2	65.6 ± 2.7	− 19.2	0.003
Cyclophosphamide	62.0 ± 2.5	66.0 ± 3.0	− 6.1	0.306	59.1 ± 2.7	60.0 ± 2.4	− 1.4	0.816	58.0 ± 5.1	61.8 ± 2.9	− 6.2	0.512

Table 1 (continued)

	March 15–May 9				May 10–July 4				July 5–August 29			
	2020	2017–2019	% change	*p* value	2020	2017–2019	% change	*p* value	2020	2017–2019	% change	*p* value
Cytoxan	47.1 ± 1.5	62.5 ± 2.7	− 24.5	< 0.001	45.8 ± 2.7	57.5 ± 2.1	− 20.4	0.001	50.0 ± 3.6	63.7 ± 3.3	− 21.5	0.005
Tacrolimus	68.1 ± 2.4	60.5 ± 2.5	+ 12.6	0.030	70.4 ± 3.6	64.2 ± 2.8	+ 9.5	0.182	80.5 ± 3.4	68.1 ± 2.8	+ 18.2	0.005
Prograf	42.1 ± 2.6	61.1 ± 2.6	− 31.1	< 0.001	51.1 ± 1.4	56.0 ± 2.5	− 8.8	0.090	55.9 ± 4.8	56.2 ± 2.7	− 0.6	0.952
Cyclosporine	68.1 ± 3.7	71.4 ± 1.7	− 4.6	0.417	73.9 ± 3.0	68.3 ± 1.6	+ 8.1	0.104	65.9 ± 1.9	71.5 ± 1.6	− 7.8	0.021
Gengraf + Neoral + Sandimmune	32.1 ± 4.8	44.6 ± 3.0	− 28.0	0.026	30.6 ± 1.9	43.2 ± 2.8	− 29.1	< 0.001	31.1 ± 4.4	44.4 ± 3.5	− 29.9	0.018
Tocilizumab	71.6 ± 6.8	5.3 ± 0.3	+ 1253.5	< 0.001	26.5 ± 1.0	5.0 ± 0.5	+ 434.4	< 0.001	25.0 ± 3.2	5.0 ± 0.4	+ 400.0	< 0.001
Actemra	57.8 ± 7.4	10.6 ± 0.6	+ 443.6	< 0.001	21.1 ± 1.8	11.3 ± 0.6	+ 87.1	< 0.001	18.4 ± 1.5	11.4 ± 0.6	+ 61.5	< 0.001
Sarilumab	59.1 ± 8.4	10.9 ± 1.2	+ 442.5	< 0.001	9.9 ± 1.5	9.9 ± 1.4	− 0.1	0.995	9.5 ± 1.2	9.2 ± 0.9	+ 3.5	0.829
Kevzara	48.4 ± 9.0	13.0 ± 1.2	+ 272.2	< 0.001	15.5 ± 1.8	14.5 ± 1.2	+ 6.9	0.650	13.9 ± 2.3	11.1 ± 0.9	+ 25.1	0.249
Anakinra	63.1 ± 7.0	21.9 ± 1.8	+ 188.6	< 0.001	44.0 ± 5.8	23.0 ± 1.7	+ 91.0	< 0.001	43.4 ± 3.3	25.3 ± 2.1	+ 71.2	< 0.001
Kineret	54.8 ± 6.8	40.6 ± 3.5	+ 34.9	0.064	44.1 ± 6.5	40.4 ± 4.2	+ 9.3	0.626	30.9 ± 4.7	38.0 ± 3.1	− 18.8	0.206
Canakinumab	4.0 ± 0.6	4.1 ± 0.3	− 1.3	0.046	4.3 ± 0.6	5.3 ± 0.5	− 18.7	0.215	4.2 ± 0.4	4.2 ± 0.5	+ 0.2	0.989
Ilaris	17.5 ± 3.0	25.9 ± 2.5	− 32.5	0.029	29.4 ± 5.2	22.1 ± 2.1	+ 33.0	0.197	20.9 ± 2.4	24.7 ± 2.2	− 15.6	0.232
Rilonacept	28.7 ± 2.1	33.4 ± 0.2	− 14.2	0.023	27.3 ± 0.5	34.8 ± 0.2	− 21.6	< 0.001	48.3 ± 15.4	42.4 ± 6.8	+ 13.9	0.726
Arcalyst	38.3 ± 4.4	42.5 ± 0.3	− 9.8	0.339	62.0 ± 8.4	45.4 ± 0.7	+ 36.7	0.049	37.0 ± 0.0	65.3 ± 8.0	− 43.4	< 0.001
Etanercept	50.4 ± 2.7	51.5 ± 3.2	− 2.3	0.780	40.0 ± 4.8	53.1 ± 3.7	− 24.7	0.029	37.5 ± 4.3	47.4 ± 2.8	− 20.9	0.055
Enbrel	33.1 ± 2.5	35.5 ± 0.9	− 6.8	0.367	27.3 ± 1.0	36.3 ± 2.9	− 24.8	0.004	28.5 ± 1.6	35.5 ± 1.0	− 19.6	< 0.001
Infliximab	77.5 ± 3.6	65.0 ± 2.5	+ 19.2	0.005	62.6 ± 3.4	58.3 ± 3.8	+ 7.4	0.400	74.0 ± 3.4	55.8 ± 3.0	+ 32.6	< 0.001
Remicade	66.9 ± 3.8	76.0 ± 1.8	− 12.0	0.031	58.1 ± 3.1	77.1 ± 1.9	− 24.6	< 0.001	64.1 ± 3.1	79.2 ± 2.2	− 19.0	< 0.001
Adalimumab	51.9 ± 5.1	57.8 ± 2.9	− 10.2	0.316	51.8 ± 2.2	51.1 ± 3.3	+ 1.3	0.866	59.6 ± 4.5	48.9 ± 3.2	+ 22.0	0.054
Humira	65.2 ± 5.5	66.2 ± 2.0	− 1.4	0.870	57.5 ± 2.4	68.0 ± 2.5	− 15.4	0.002	63.0 ± 2.3	70.8 ± 2.0	− 11.0	0.010
Certolizumab	20.8 ± 4.8	29.4 ± 2.3	− 29.2	0.108	20.9 ± 2.4	21.8 ± 1.8	− 4.2	0.764	21.6 ± 2.2	29.9 ± 3.0	− 27.8	0.027
Cimzia	61.0 ± 5.7	59.0 ± 3.2	+ 3.4	0.760	64.5 ± 4.4	61.9 ± 2.5	+ 4.2	0.605	63.6 ± 4.6	61.3 ± 2.5	+ 3.8	0.658
Golimumab	22.9 ± 2.4	36.5 ± 4.2	− 37.2	0.005	24.0 ± 4.1	40.0 ± 3.2	− 40.0	0.002	32.5 ± 1.9	30.9 ± 3.2	+ 5.3	0.660
Simponi	50.8 ± 1.8	57.0 ± 3.2	− 11.0	0.085	53.6 ± 2.5	61.1 ± 2.7	− 12.3	0.042	54.9 ± 4.4	62.3 ± 2.9	− 11.8	0.162
Secukinumab	45.4 ± 2.5	39.8 ± 3.2	+ 14.0	0.173	38.9 ± 5.2	46.5 ± 3.8	− 16.4	0.237	30.5 ± 3.9	42.2 ± 4.1	− 27.7	0.039
Cosentyx	40.9 ± 1.4	37.2 ± 2.6	+ 9.9	0.217	41.8 ± 1.4	38.2 ± 1.7	+ 9.3	0.116	38.1 ± 1.4	44.4 ± 2.0	− 14.2	0.011
Ixekizumab	31.9 ± 4.4	47.3 ± 3.8	− 32.7	0.008	41.3 ± 6.2	48.8 ± 3.6	− 15.5	0.294	35.3 ± 2.9	50.0 ± 4.3	− 29.6	0.005
Taltz	45.5 ± 2.3	65.6 ± 2.9	− 30.7	< 0.001	46.9 ± 1.7	59.8 ± 4.1	− 21.6	0.004	48.9 ± 3.7	53.6 ± 3.8	− 8.9	0.371
Ustekinumab	37.6 ± 4.2	37.0 ± 2.7	+ 1.8	0.894	40.0 ± 6.9	45.8 ± 3.0	− 12.7	0.439	37.3 ± 3.5	38.8 ± 2.2	− 4.0	0.712
Stelara	69.8 ± 2.4	61.3 ± 2.5	+ 13.8	0.015	62.0 ± 2.6	61.1 ± 1.9	+ 1.5	0.774	73.0 ± 3.3	68.1 ± 1.8	+ 7.2	0.189
Guselkumab	38.5 ± 3.0	46.7 ± 3.1	− 17.5	0.062	45.8 ± 4.7	47.4 ± 3.7	− 3.4	0.789	49.5 ± 6.4	47.9 ± 3.4	+ 3.3	0.827
Tremfya	37.9 ± 2.9	40.8 ± 2.9	− 7.2	0.470	32.4 ± 2.6	36.1 ± 4.8	− 10.3	0.494	48.6 ± 2.8	39.2 ± 2.8	+ 24.0	0.017

Table 1 (continued)

	March 15–May 9				May 10–July 4				July 5–August 29			
	2020	2017–2019	% change	*p* value	2020	2017–2019	% change	*p* value	2020	2017–2019	% change	*p* value
Abatacept	46.1 ± 4.1	48.9 ± 3.5	− 5.7	0.604	48.3 ± 5.8	37.3 ± 3.0	+ 29.5	0.091	52.6 ± 5.0	45.8 ± 4.6	+ 14.9	0.316
Orencia	67.3 ± 3.9	68.5 ± 2.5	− 1.8	0.789	71.5 ± 4.4	62.8 ± 2.4	+ 13.8	0.081	74.5 ± 4.0	68.6 ± 2.7	+ 8.6	0.219
Rituximab	63.4 ± 3.4	70.7 ± 3.0	− 10.3	0.106	68.3 ± 3.9	70.5 ± 2.0	− 3.1	0.611	70.9 ± 4.6	76.2 ± 2.2	− 7.0	0.293
Rituxan	46.9 ± 3.6	71.5 ± 2.2	− 34.4	< 0.001	53.0 ± 2.6	70.7 ± 2.1	− 25.0	< 0.001	57.3 ± 2.0	73.5 ± 2.1	− 22.1	< 0.001
Belimumab	23.4 ± 2.3	25.2 ± 2.3	− 7.3	0.573	23.8 ± 3.1	24.3 ± 2.0	− 2.2	0.888	24.0 ± 5.2	25.7 ± 2.3	− 6.6	0.767
Benlysta	48.5 ± 3.0	48.8 ± 3.2	− 0.5	0.954	54.0 ± 2.8	51.5 ± 3.8	+ 4.8	0.598	52.0 ± 2.2	52.9 ± 3.4	− 1.7	0.831
Tofacitinib	34.4 ± 2.7	35.0 ± 2.7	− 1.8	0.869	31.3 ± 2.5	40.0 ± 2.5	− 22.0	0.012	32.6 ± 3.2	44.5 ± 3.5	− 26.8	0.012
Xeljanz	48.3 ± 3.0	49.7 ± 3.6	− 2.9	0.763	44.6 ± 2.3	45.1 ± 2.3	− 1.1	0.878	47.1 ± 2.0	47.6 ± 1.9	− 1.0	0.871
Baricitinib	52.9 ± 10.2	27.6 ± 5.2	+ 91.9	0.027	47.8 ± 7.2	18.9 ± 1.7	+ 153.2	< 0.001	30.4 ± 3.7	16.1 ± 1.6	+ 88.2	< 0.001
Olumiant	31.5 ± 9.5	32.4 ± 3.9	− 2.7	0.933	42.0 ± 5.0	29.4 ± 3.5	+ 42.8	0.039	28.6 ± 3.8	31.0 ± 3.0	− 8.0	0.609
Apremilast	14.0 ± 2.2	17.4 ± 1.7	− 19.5	0.227	20.1 ± 2.0	17.7 ± 1.8	+ 13.7	0.359	18.8 ± 2.8	17.7 ± 2.0	+ 6.1	0.751
Otezla	68.9 ± 6.0	63.2 ± 3.2	+ 9.0	0.402	63.3 ± 4.6	66.3 ± 2.9	− 4.6	0.579	60.3 ± 3.6	68.9 ± 3.2	− 12.6	0.073

Plus-minus values are presented as means ± standard error (generalized estimating equations). *NSAIDs*, non-steroidal anti-inflammatory drugs

colchicine, tocilizumab, and anakinra may be attributed to media coverage of scientific studies investigating these drugs as potential therapeutic agents for the COVID-19 [32–37]. This finding also indicates that the general public has informational needs for these drugs. Given that the evidence on their efficacy, safety, or use for COVID-19 has been evolving, we recommend readers to refer to the recent version of National Institutes of Health (NIH) and Infectious Diseases Society of America (IDSA) treatment guidelines regarding the treatment and management of COVID-19 [14, 15].

In the initial period (March 15–May 9, 2020), the RSV of the term "NSAIDs" showed a statistically significant increase in RSV. Although statistically insignificant, the RSV of ibuprofen has also increased 73% in this period compared to the preceding 3 years. Between March and April 2020, the WHO provided a series of recommendations for the use of NSAIDs to treat COVID-19 that garnered public attention. In March 2020, the WHO initially advised against using ibuprofen to treat COVID-19 [38]; however, they later updated its recommendation by tweeting, "based on currently available information, WHO does not recommend against the use of ibuprofen" [39]. In April 2020, WHO published an overview on the use of NSAIDs in patients with COVID-19 [40]. Therefore, the initial trends observed in NSAIDs searches might be due to the discussions on the use of NSAIDs in patients with COVID-19.

It is notable that the RSV of brand names of immunosuppressive agents (i.e., mycophenolate mofetil, azathioprine, cyclophosphamide, tacrolimus, and cyclosporine) was reduced during the COVID-19 period compared to 2017–2019. It can be speculated that these agents have been initiated/added to the treatment regimens of patients with a rheumatic disease less often during the COVID-19 period, as these drugs have previously been associated with an increased risk of certain viral infections [41]. However, this assumption needs further validation. The more likely explanation for the observed decrease is that these drugs were initiated/prescribed less frequently during the COVID-19 period due to a general decrease in transplant surgeries [42] as these drugs are also used to prevent tissue rejection after an organ transplant. The decrease in the initiation of these drugs may lead to an observed decrease in RSV of these drugs, as patients who were prescribed a new immunosuppressive drug may search for online information. This presumption requires confirmation as well. Additionally, to our knowledge, it should be noted that there is currently no evidence on a possible association between an increased risk of COVID-19 and these immunosuppressive agents. Furthermore, the American College of Rheumatology (ACR) guidelines regarding the management of rheumatic diseases during the COVID-19 pandemic (version 2) recommend that conventional (DMARDs), immunosuppressants, biologics, JAK inhibitors, and NSAIDs may be continued in patients with stable rheumatic disease in the absence of COVID-19 infection or SARS-CoV-2 exposure [9]. However, as the literature is rapidly evolving, we recommend readers to refer to the recent version of ACR, European League Against Rheumatism (EULAR), and African League Against Rheumatism (AFLAR) guidelines on the management of rheumatic diseases during the COVID-19 pandemic [9, 10, 43].

Previous studies investigated the population-level interest in several treatment approaches during the COVID-19 era [25–28]. Bhambhvani et al. examined the population-level interest in elective urology procedures categorized into 4 categories: male infertility, erectile dysfunction, Peyronie's disease, and vasectomy. They showed a decrease across all categories in the 30 days prior to March 18, 2020, period compared to 30 days after and March–May 2020 period compared to January 2015–February 2020 [25]. Jella et al. showed a decrease in population-level interest in knee and hip arthroplasties during March 2020, which breeched the lower control limit of previous 5 years [26]. In a study investigating population-level interest in facial plastic surgery from January 1, 2020, to July 10, 2020, Dhanda et al. showed a significant decrease during March–April 2020 compared to January–February 2020 [27]. Guzman and Barbieri examined the population-level interest in cosmetic procedures. They showed a statistically significant decrease in March 15–29, 2020, period compared to April 28, 2019,–March 8, 2020 (pre-pandemic period) [28]. All these previous studies showed a decrease in interest in treatment approaches investigated. Distinct from these previous studies investigating the procedural treatments, our study investigated pharmacological treatments (i.e., anti-rheumatic drugs). Also, as our study was conducted later, it was able to include a wider period of 2020. Therefore, it provides information not only on initial stage but also on short-term interest.

Limitations

Our study has some limitations. We used Google Trends, which captures the search behavior of people using the Google search engine, exclusively. However, it most likely represents American search queries because the Google search engine accounts for over 85% of all internet search volume in the USA [44]. Furthermore, because Google Trends does not provide demographic characteristics of the people who search on Google, the interest cannot be assessed by stratifying specific subpopulations. Therefore, our results can only be applied to the general population. Also, to control for possible seasonal variation in the searches [18, 20], we compared the COVID-19 period to preceding years (as similarly performed in previous studies [25, 26]); however, this approach may also introduce a limitation. The observed differences might be caused by decreases/increases in searches in

2017–2019 (e.g., Food and Drug Administration warning on Uloric in 2019 [45]). Therefore, our results should be interpreted with caution and need to be verified by further studies. Despite these limitations, our study would contribute to the knowledge on Google searches of anti-rheumatic drugs during the COVID-19 pandemic.

Conclusion

There were significant increases in RSV of colchicine, hydroxychloroquine, tocilizumab, and anakinra during both initial and short-term COVID-19 periods when compared to overlapping periods of the preceding 3 years reflecting a heightened level of information-seeking on these drugs during the pandemic. Rheumatologists should address this increase in informational demand. Further research assessing medium- and long-term interests in anti-rheumatic drugs is required to increase our knowledge on this new pandemic.

Authors' contributions Conception of the study: SK; collection, analysis, and/or interpretation of data: SK, ASK, HP, RR, and MK; drafting the manuscript: SK; critically revising and editing the manuscript: SK, ASK, HP, RR, and MK; final approval for submission: SK, ASK, HP, RR, and MK.

Data availability The data are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest SK received congress travel, accommodation, and participation fee support (12th Anatolian Rheumatology Days) from Abbvie. The other authors have no conflict of interest in this study.

Ethics approval NA

Consent to participate NA

Consent for publication NA

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