Trends and Development in Clinical Research of FDA-Approved Drugs Against Interleukin-1 β : A Bibliometric Analysis.

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Research

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Abstract

Background

Interleukin(IL)-1 β is a promising target for many diseases such as atherosclerosis, rheumatoid arthritis and cancer because it has been found to involve in the development of diseases. Anakinra, Canakinumab and Rilonacept were three Food and Drug Administration (FDA)-approved drugs and used for inhibiting IL-1 β . Our study aims to access the trends and development for IL-1 β inhibitors using bibliometric analysis.

Methods

All publication records were obtained from databases Web of Science and Pubmed. Publishing characteristics including organization, author, journals and co-authorship, Keywords, co-occurrence network, related journals network were analyzed by VOSviewer 1.6.16 (by Leiden University) and Bibliometric package in R(4.0.5). Graph prism 8 was used to performed descriptive analysis of all data.

Results

274 publications were enrolled in our study. Of the three drugs, anakinra has been extensively studied, with 130 publications related to it between 1997 and 2021. Clinical studies on IL-1 β antagonists mainly focused on rheumatoid arthritis. Non-inflammatory diseases such as cardiovascular disease and cancer were also found in the related clinical research. The United States published the most articles in clinical research on IL-1 β inhibitor and it was the country that participated in the most collaborations.

Conclusion

Targeting IL-1 β was still a hot spot for clinical research in inflammatory diseases. As progresses are made in the field, Canakinumab and Rilonacept as two novel inhibitors, will increase in a similar trend to that of Anakinra. The number of studies about the inhibitors targeting IL-1 β in inflammatory diseases will emerge more in the future. Cancer therapy might be the trend in the clinical studies of antagonizing IL-1 β .

1. Introduction

Interleukin- 1 β (IL-1 β), a complex family of cytokines, has been being explored for decades. Not only does IL-1 maintain homeostasis and interact with innate and adaptive immunity, but it also plays a role in many pathological processes(1). According to the molecular structure, IL-1 are classified into three categories: secreted molecules with agonistic activity, receptor antagonists and anti-inflammatory cytokines (2). Belonging to the first subgroup, IL-1 β is not secreted from hematopoietic cells into the extracellular matrix as an active form until caspase-1 or other appropriate enzymes cleaves the inactive precursor(3). Free IL-1 β binds to IL-1 receptor 1 (IL-1R1) and then gradually pro-inflammatory signal will

be initiated(1). To some extent, inflammation is a double-edged sword. Once the release of IL-1 β gets out of control, inherited or nonhereditary autoinflammatory diseases occur, such as Schnitzler syndrome, systemic-onset juvenile idiopathic arthritis and adult Still disease(4). Previously smooth vascular walls influenced by IL-1 β -related inflammation get damaged, and then it's more susceptible to evolve into atherosclerosis and other cardiovascular pathological state(5). Tinna Christersdottir et al. (6) discovered that after mice having radiation-induced vascular inflammation were given the IL-1 receptor antagonist, anakinra, inflammatory mediators were ameliorated. In previous study, IL-1 β was observed to have a negative effect on neurogenesis and synaptic plasticity, leading to cognitive dysfunction(7). Association between cancer and cytokines has attracted much attention. IL-1 β participates in primary carcinogenesis and subsequent proliferation, and it also contributes to survival and metastasis of malignant cells (8, 9). Interestingly, Irena Kaplanov and his team observed that IL-1 β -deficient mice or administration of IL-1 β neutralization had a negative effect on Murine 4T1 Mammary Carcinoma (10). Last but not least, in the research of Chien-Chung Huang et al. (11), it was revealed that melatonin reduced the production of IL-1 β in human synovial fibroblasts and protected rheumatoid arthritis mouse model from cartilage degradation.

Not surprisingly, IL-1 β has been a promising target for autoinflammatory, autoimmune diseases and other diseases. Strategy for blocking IL-1 β has been carried out during clinical practice. Take following autoinflammatory disorders with gene mutation causing excessive IL-1 β secretion as examples. After patients diagnosed with the Muckle-Wells syndrome were treated with anakinra, a recombinant IL-1 receptor antagonist which could block both IL-1 α and IL-1 β , symptoms were obviously relieved (12, 13). Patients who had Cryopyrin-Associated Periodic Syndromes (CAPS) took riloncept (a chimeric recombinant fusion protein neutralizing IL-1 α and IL-1 β) (14) or Canakinumab (anti-IL-1 β antibody)(15) in clinical trials, and eventually came to better outcomes. Moreover, there are abundant clinical trials studying IL-1 β blockade on diseases in different fields. The CANTOS trial (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) (16) showed that Canakinumab was beneficial in reduction of cardiovascular events. In current clinical practice, anakinra, riloncept and Canakinumab have been approved for clinical application, such as rheumatoid arthritis, CAPS, Tumor necrosis factor receptor-associated periodic syndrome and etc(17). Since IL-1 β covers a broad span within pathology, considerable researches about the effect of IL-1 β blockade on various diseases are undoubtedly meaningful to be done.

In this study, we utilized bibliometric analysis to assessed scientific papers from the Web of Science (WOS) and PubMed databases for all clinical studies on IL-1 β inhibitors. Assessment of the trends and development for IL-1 β inhibitors help better understand the emerging trends, focus and hotspots of inhibiting IL-1 β research through analyzing publication journals, institutions citations and authors of published studies

2. Materials And Methods

Data source and search strategy

All publication records were obtained as plain texts from Web of Science and PubMed databases on August 28, 2021. We first performed a PubMed database search using the following data retrieval strategy: (ILARIS OR Canakinumab OR anakinra OR Kineret OR Rilonacept), article type: Clinical trial; We next searched WOS using the following search string: (TS=(ILARIS OR canakinumab OR anakinra OR Kineret OR Rilonacept) AND TS= ("clinical trial*" OR "clinical stud*" OR "clinical research*")), DOCUMENT TYPES:Article; LANGUAGE:ENGLISH, (Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED).

Qi Tan and Zimo Yang search the publication records and extracted data independently. Clinical research(Prospective study and Retrospective study) on IL-1 β inhibitors, case reports on the efficacy of IL-1 β inhibitors and Meta-analysis of clinical research on IL-1 β inhibitors are incorporated into our analysis. Publishing characteristics including organization, author, journals and co-authorship were analyzed by VOSviewer 1.6.16 (by Leiden University) and Bibliometric package in R(4.0.5).

Graph prism 8 was used to performed descriptive analysis of all data. Keywords, co-occurrence network, related journals network were performed by VOSviewer 1.6.16 (by Leiden University).

3. Results

3.1 General analysis of the trend of three FDA-approved IL-1 β inhibitors

After retrieving publications from WOS and PubMed, we found out 194 in WOS and 259 in pubmed, which amounted to 280 articles, and where there were 174 publications about Anakinra, 77 about Canakinumab, and 29 about Rilonacept. All of the qualified articles were published from 1997 to 2021. In 1997, the first literature related to clinical research appeared. Over the first decade (1997-2007), there were less than 10 publications, and later (2008-2021) the number was averagely raised and stabilized at about 17.

3.1.1 General analysis based on countries

According to the countries publishing relative papers, Figure 2A revealed that the top 10 were America, Britain, Italy, Germany, France, Switzerland, Greece, Netherlands, China and Ireland, among which America ranked the first with 123. Apart from America and China, the remainder were from Europe, indicating that Europe paid much more interest and attention to clinical research on IL-1 β inhibitors. Furthermore, statistical analyses about quotation rates of articles from various countries showed that the top 3 were Switzerland, Denmark and America, of which total quotation rates were 138.53, 85.25, 83.8 respectively(Figure 2B). Interestingly, although America was ranked number one for the quantity of papers, its quotation rate didn't remain the top. Denmark didn't join the top 10 for the number of articles, but it was among the top list of total quotation rates, which revealed that clinical study on IL-1 β inhibitors in Denmark was impactful to an extent and was worth to be learnt from. Figure 2C showed that country cooperation changed over time. The size of nodes in Figure 2D stood for number of countries cooperating

with each other, and it appeared that America gained the highest number which had 20 nodes. Before 2014, international collaborations concentrated on America, British, France, Switzerland and etc. As time passed by, Japan, Turkey, Spain and other countries joined inter-state work. After 2017, the cooperation of China with other nations made evident progress, which indicated that this kind of clinical study had rising appeal to various countries.

3.1.2 General analysis based on institutions

Figure 3A exhibited the top 10 publishing numbers of scientific institutions, concentrating in America and Europe. Virginia Commonwealth University had the highest publishing number. Interestingly, the research department of drug company Novartis occurred among the top 10, indicating the potential market and pharmaceutical value of these inhibitors. In figure B&C, network diagrams illustrated that institutions collaborated with each other, which also showed the top 10 institutions, for instance, Regeneron Pharmaceut Inc, Amgen Inc and Novartis Pharmaceut, with the largest total link strength. These 3 companies had been working with some well-known institutions in universities. From the information in the column chart, Novartis Pharmaceut had the greatest number of cooperation and the strongest total link strength. Among research institutes from universities, Virginia Commonwealth University reached the widest cooperation, which reflected the important status in the field of associated study.

3.1.3 General analysis of journals

Figure 4A illustrated the top 10 journals with the leading publication numbers. Annals of the Rheumatic Disease ranked the first visibly. Since inhibitor of IL-1 β was the most efficient strategy to treat arthritis, the results mentioned above revealed that arthritis played a major role in clinical study on IL-1 β inhibitors. Figure 4B showed the top 10 journals with considerable local citation times (LCT), the New England Journal of Medicine, Arthristis and Arthritis Reheum ranked the top 3, surpassing ann rheum dis, and the higher LCT implied the higher impact in the field of relative researches. Figure 4C represented for journal co-citation network map separated into three clusters. Circulation and the New England Journal of Medicine were the biggest nodes in blue and red cluster respectively, and Arthritis Rheum and Annals Of The Rheumatic Diseases shared the main point in the green cluster. In the network, the major co-citation journals were the New England Journal of Medicine (total link strength=7853), Circulation (total link strength=7175), Annals Of The Rheumatic Diseases (total link strength=8733) and Arthritis Rheum (total link strength=8582), implying that they were highly-qualified journals in this study field.

3.1.4 General analysis of manuscripts

The results in Table1 showed the top 10 most cited articles and accordingly in network chart (Figure 5A), they showed research values. The bigger nodes were, the largerer citations were. The article entitled "Interleukin-1-receptor antagonist in type 2 diabetes mellitus" published in the New England Journal of Medicine in 2007 occupied the first position, which benefited the previous result that the New England Journal of Medicine was at the top of the list of total citations and reflected the clinical value again. Network diagram showing keywords changing over time (Figure 5B) revealed that Anakinra was the most widely studied among three drugs, and rheumatiod arthritis was the most researched disease. In early

studies, researches about IL-1 β inhibitors focused on the function with Tumor Necrosis Factor (TNF), rheumatoid diseases and other aspects. After 2016, the focus was shifted to drug safety, efficiency and inflammation-related factors, such as c-reactive protein and so on. Currently, emerging studies concentrated on cardiovascular diseases, including myocardial infarction, atherosclerosis and heart failure. Therefore, clinical research on IL-1 β inhibitors gained diversity and a variety of diseases were involved.

Table 1
Top 10 most Locally cited articles

Title	Year	Journal	Local citation Times
Use of canakinumab in the cryopyrin-associated periodic syndrome	2009	N Engl J Med	38
Interleukin-1-receptor antagonist in type 2 diabetes mellitus	2007	N Engl J Med	23
Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis	2012	N Engl J Med	23
Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies	2008	Arthritis Rheum	21
Interleukin-1 β inhibition and the prevention of recurrent cardiovascular events: rationale and design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)	2011	Am Heart J	18
Canakinumab for the treatment of acute flares in difficult-to-treat gouty arthritis: Results of a multicenter, phase II, dose-ranging study	2010	Arthritis Rheum	16
A pilot study of IL-1 inhibition by anakinra in acute gout	2007	Arthritis Res Ther	13
Interleukin-1 blockade with anakinra to prevent adverse cardiac remodeling after acute myocardial infarction (Virginia Commonwealth University Anakinra Remodeling Trial [VCU-ART] Pilot study)	2010	Am J Cardiol	13
Enhanced interleukin-1 activity contributes to exercise intolerance in patients with systolic heart failure	2012	PLoS One	13
A phase II, multicenter, open-label study evaluating dosing and preliminary safety and efficacy of canakinumab in systemic juvenile idiopathic arthritis with active systemic features	2012	Arthritis Rheum	13

3.1.5 General analysis of authors

Authors ranking the top 10 with substantial article quantity and total local citations, were listed in Figure 6A&B. Abbate got the top spot at the both lists, 25 and 91, respectively. What was worth mentioning here was that articles of authors Kone and Quartier had remarkable citation achievement and their impact couldn't be neglected, although their articles remained a small quantity. Network graph about author co-citation in Figure 6C was separated into 4 areas, where red cluster was the largest. Among all of the nodes, the biggest node appeared in Dinarello CA, Ridker PM, whose citation value was up to 136,125, apparently exceeding other authors. Total link strength (632) of Dinarello was the strongest amongst all nodes, indicating the most influential role in the field. What's more, the author cooperation network graph was shown in Figure 6D, and there were three main sets. The biggest one was in green. Collaboration between three sets was limited, which implied that large number of researchers had stable cooperators.

3.2 General analysis of the trend of Anakinra

According to our analysis of sub-groups, research on Anakinra was started from 1997, and it was worth noting that publishing tendency was close to inhibitors. However, the study on Canakinumab and Rilonacept was initiated in 2008, which meant that Anakinra kept active and was widely studied in the area of clinical researches focusing on IL-1 β inhibitors from 1997 to 2007. In spite of the development of Canakinumab and Rilonacept, published papers of Anakinra still kept over 5 each year and even reached a peak in 2016, except 2008 and 2013, in which publication outputs were 11 and 5 respectively (Figure 7A). Figure 7B displayed the lists of top 10 countries with high published articles and average article citation. America ranked first with 61 papers, far beyond other countries, indicating that America put much effort into this kind of researches, and the remainder was almost European countries. Moreover, the effort China had been investing into scientific research was increasing. In the aspect of citation, citation quantity in Switzerland (225) was obviously higher than that in America (88.77), which reflected that research findings in Switzerland tended to be widely approved with stronger influence. Although China scraped into top 10 published papers, its average article citation wasn't satisfactory. On the contrary, Denmark was the third in order of average article citation with not too many articles, indirectly showing its potential impact. Figure 7C illustrated network graph of national collaboration over time. America had the most partner, such as Germany. In the early stage, cooperation among countries mainly appeared in Germany, America, Denmark, Ireland and etc. As time passed by, Switzerland, Sweden and Greece also initiated work on related researches together with other countries. China and Italy didn't join inter-state collaboration until 2016, with fewer partners, reflecting that they were aware of the importance of international clinical trials. The network (Figure 8D) involved 3 clusters labeled in different colors. Node standing for Circulation was the biggest one in blue. Arthritis Rheum and Ann Rheum Disease were the two major nodes in green, and the New England Journal of Medicine dominated red nodes. In this network, the New England Journal of Medicine (total link strength=3849), Circulation (total link strength=4348) and Annals Of The Rheumatic Diseases, (total link strength=5667) were 3 primary co-cited journals, corresponding to preceding general tendency, which proved that Anakinra stayed a dominant position in researches around IL-1 β inhibitors. Keywords in researches on Anakinra were displayed in the heatmap (Figure 7G). Rheumatoid arthritis appeared to be the primary disease associated with the study. Inflammation was one of the hottest topics as well, and the function of

Anakinra as an IL-1 receptor antagonist was explored. Among clinical trials correlating with Anakinra, there existed multicenter and double-blind trials. Bar chart from Figure 8H listed authors with the top published quantities. Top 2 authors were Abbate (19 articles), Van Tassell BW (18 articles), obviously exceeding others. Figure 8i was a network chart displaying author cooperation over time, where Abbate Antonio and Vantassel Benjamin had the most partners. In the early stage, collaborators including abate, Van Tassell, Biond-zoccai and Dinarello seemed to be critical contributors and kept dedicating themselves to this area. The top 10 journals with outstanding published articles were listed in Figure 7E. Annal of the Rheumatic Diseases (12 articles) ranked first and difference among them was not significant, indicating that researchers tended to submit articles to the former journal.

3.3 General analysis of the trend of Canakinumab

We found out 77 articles were related to clinical study on Canakinumab from 2009 to 2021. The first paper emerging in 2009 was entitled "Use Of Canakinumab In The Cryopyrin-Associated Periodic Syndrome". Between 2010 and 2021, 6 articles were published on average each year. Yearly publication quantity reached a peak in 2020 (13 articles). Figure 8C displayed countries with the number of papers and citations. America ranked first with 39 published papers, far ahead of other countries, reflecting that America also invested lots of resources into such kind of drug in clinical trials. However, British won average article citation with the highest point of 194.3, more than America (89.8), indicating its high quality and deep influence in such area. According to the network graph shown in Figure 8D, we could know about the change of international cooperation over time. America and Switzerland had the top 2 numbers of cooperation with other nations. From the time-varying figure, British, France and Turkey cooperated together in 2015, which was earlier than America, Switzerland and Germany. After 2018, Hungary, Canada and Israel joined cooperation, emphasizing the clinical research about IL-1 β inhibitors. What they had been discovering might push progress in this drug for clinical use. Furthermore, from the bar chart shown in Figure 8E, Annal of the rheumatic diseases was at the head of the top 10 journals with 10 articles through our retrieval. Co-citation chart (Figure 8F) consisted of two clusters. Green one consisted largely of the New England Journal of Medicine, while the red one was primarily composed of Arthritis Rheum and Annals Of The Rheumatic Diseases, indicating high and good reputation of these three journals. Green nodes were less than red ones. Take a look at the next chart (Figure 8G) which included keywords about Canakinumab-related clinical studies. These researches were manifested in the aspects of inflammation, efficacy and safety. The keyword chart was separated into three clusters. Efficacy and Anakinra dominated red and blue nodes, respectively, and red ones consisted mainly of inflammation and C-reactive protein. In the clinical researches on Canakinumab, some were similar to those related to Anakinra, or both Canakinumab and Anakinra occurred in the same study. In addition, Thuren and Ridker were top 2 authors who delivered 20 and 18 articles separately, manifestly beyond others (Figure 8H). According to author cooperation network chart (Figure 8I), there were two sets, which were independent of each other. Kuemmerle and Queartier were the main authors joining cooperation in the early phase, while after 2019 author collaboration was primarily centralized in Glynn, Macfadyen and Everette.

3.4 General analysis of the trend of Rilonacept

A total number of 297 articles about clinical researches on Riloncept from 2008 to 2020 were accepted in our study. Unexpectedly, there was no paper about Riloncept in 2015, 2016 and 2018. Publication got a peak in 2012 with 5 articles (Figure 9A). America got the largest proportion of publishing articles once again with a number of 23, and America (citation score: 66) and Germany (citation score: 60.4) remained top 2 average article citation (Figure 9C). Additionally, Israel and North Africa reached 45.3 and 53 citation scores, respectively. Interestingly, Germany only published one related paper but had high citation, which meant that it played a critical role in Riloncept's clinical study. Since America paid much effort in this field, it stayed ahead. In Figure 9D, it was shown that Germany, America and Ireland were some of the pioneers who cooperated with each other, and America ranked first in the network of cooperation mainly from 2010 to 2012. China and Italy did not occur in cooperative groups until 2016. As the cooperative relationship changed over time, British, France and Turkey collaborated in 2015, earlier than America, Switzerland and Germany. Hungary, Canada and Israel participated together in clinical research since 2018. All of the researches might promote exploration of Riloncept as IL-1 β inhibitors. Then, Figure 9E illustrated the top 10 journals with high number of published papers. Annals of the Rheumatic Diseases stayed at the first position with 4 papers, followed by Rheumatology with 3 papers. The difference among journals was not manifest, due to a small number of total published articles. Keyword chart around Riloncept in Figure 9F displayed only 5 nodes because of small retrieved results. Keywords such as management and double blind, newly emerged, while in early phase inflammation and disease dominated nodes of keywords. In the aspect of authors, Weinstein and Schumacher were top 2 authors with high publication outputs (9 and 7 respectively), and other authors in the top 10 list had around 4 papers (Figure 9G). From the graph including local article citation of each author (Figure 9H), citation times of Weinstein and Vancopoulos were more than 20. Weinstein's published articles and citation times occupied the first position through statistics, revealed that his scientific outcomes deserved attention.

4. Discussion

We analyzed 274 publications in our study. Of the three drugs, Anakinra has been extensively studied, with 130 publications related to it between 1997 and 2021. As progresses are made in the field, Researches about the two novel inhibitors, Canakinumab and Riloncept, will increase in a similar trend to that of Anakinra. Clinical studies on IL-1 β antagonists mainly focused on rheumatoid arthritis. There were also studies associated with their applications in cardiovascular disease (atherosclerosis, heart failure, etc.) and cancer. The United States published the most articles in clinical research on IL-1 β antagonists and it was the country which participated in the most collaborations. More and more countries gradually paid attention to clinical studies of IL-1 β inhibitors, such as China, Italy.

IL-1 β is involved in the development of many diseases, such as Atherosclerosis. It has been shown that IL-1 β deficiency could slow the progression of atherosclerosis.(18) IL-1 has also been shown to be associated with joint damage due to rheumatoid arthritis.(19) In animal models of rheumatoid arthritis, IL- β was observed to promote inflammation and disease through regulation of the ERK/STAT1 pathway, which made antagonism against IL-1 β one of the methods to benefit patients with rheumatoid arthritis or other Inflammatory disease. (20) Our analysis also showed that studies about rheumatoid arthritis and IL-

1 β dominated. The studies have gradually expanded to other diseases, such as cancer. It has been reported that IL-1 β played a role in tumor invasion and angiogenesis and could inhibit the growth of breast cancer cells. (21, 22) Currently, Clinical trials associated with IL-1 β have been conducted in patients with lung cancer or localized Clear Cell Renal Cell Carcinoma. (NCT03447769, NCT04028245) It is predictable that in future clinical studies, antagonism of IL-1 β will receive more and more attention in cancer treatment.

As shown in the results, the United State heavily invested in and plays a major role in the clinical researches of IL-1 β inhibitors. We supposed that the reason had to do with the broad scope of its collaborations and the availability of many high-level researchers. A lot of productive authors worked at U.S. institutions. In addition, the U.S. research institutions collaborated with different organizations, including academic institutions and commercial companies. As can be seen from the results, there were many collaborations in which Novartis joined. These collaborations between different types of institutions increased the vigor of research in this field.

There were 164 publications from 1997 to 2020 about Anakinra in our results. Articles about Anakinra were the most among the three drugs. Anakinra is a competitive inhibitor of IL-1. It could inhibit the binding of IL-1 α and IL-1 β to the receptor, thereby blocking related signaling process. (23) As researches progressed, IL-1 β was found to be a more potent mediator of inflammation than IL-1 α , playing an important role in a variety of inflammatory responses. (24) Therefore, Anakinra is more commonly associated with antagonism of IL-1 β . The keyword network for anakinra showed that its most popular area of research was relevant to rheumatoid arthritis. However, there were also other areas such as heart failure, inflammation and etc. (NCT01542502, NCT00897715). Due to a large number of studies surrounding rheumatoid arthritis, it became one of the clinical drugs approved by the FDA for the approval of the treatment of rheumatoid arthritis.

The strategy of antagonism of IL-1 β by Anakinra was to inhibit indirectly by targeting its receptor. In 2009, a human anti-il-1 β monoclonal antibody, Canakinumab, developed by Novartis for immune diseases, is designed to block IL-1 β signaling by directly binding IL-1 β , thereby reducing its effects in the inflammatory response.(25) By 2021, there were 77 clinical research articles related to this drug. Similar to Anakinra, the United States published 39 papers, which was the most among all countries. Thuren T and Ridker PM, Libby P had the most articles. In terms of research collaborations. Since the drug was first approved for application by the US FDA and the European EMEA, relevant clinical research collaborations were also between the US and European countries, especially Switzerland, due to Canakinumab approval for the treatment of cryopyrin-associated periodic syndrome early in the drug's marketing, as well as some other immune diseases. Canakinumab is also used to treat cryopyrin-associated periodic syndrome, Muckle-Wells syndrome, familial cold auto-inflammatory syndrome, and can improve the quality of patient survival. Canakinumab has also been used in oncology treatment. Clinical trials have been conducted with the combination of Canakinumab for lung cancer treatment (NCT04905316, NCT03968419)

Rilonacept is a recombinant molecule made by Regeneron. Its structure could trap IL-1 α or IL-1 β and the affinity to IL-1 β is stronger. (26) Only 29 clinical research papers were included in our study and their citation times are not much. This might be related to the fact that Rilonacept has not been available for a long time. Early studies of Rilonacept were conducted mainly in Europe and the United States, with the largest number of collaborations in the United States, which was similar to the situation of Canakinumab and Anakinra. It indicated that the influence of the United States in the field of antagonism of IL-1 β . In the keywords network, the information was limited because of the small number of articles. Rilonacept has been used in CAPS and other autoinflammatory diseases, such as type-I diabetes. (27) (NCT00962026, NCT00288704) We can also speculate that Rilonacept has the potential to be used for clinical oncology treatment as well.

The limitation of our study was that we only analyzed the literatures in English and did not include other languages. And the sources of literatures were mainly from two databases, Pubmed and Web of Science. The literatures from other databases was not included. In the process of screening the literature, some relevant articles might be missed or other irrelevant publications may be included.

5. Conclusion

By analyzing the clinical research articles of the three FDA-approved IL-1 β antagonists, we found that antagonizing IL-1 β was still a hot spot for clinical research in inflammatory diseases. We also noted that there were still many clinical studies of antagonizing IL-1 β under research. Therefore, we can infer that studies about the inhibitors targeting IL-1 β in inflammatory diseases will emerge more in the future and people will pay more attentions to their applications in cancer therapy.

Abbreviations

IL: Interleukin; CAPS : Cryopyrin-Associated Periodic Syndromes; CANTOS: Canakinumab Anti-inflammatory Thrombosis Outcomes Study; WOS: Web of Science; LCT: local citation times; TNF: Tumor Necrosis Factor; FDA: Food and Drug Administration;

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to publish

All authors have agreed to publish the final manuscript.

Availability of data and materials

All authors declare that the datasets supporting the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

All authors have no competing interests

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Authors' Contributions

Qi Tan and Zimo Yang collected and analyzed the data. Qi Tan, wenjuan Chen wrote the manuscript. Yang Jin edited and revised the manuscript. All authors have approved the final manuscript.

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Figures

Figure 1

The number of publication article of three FDA-approved IL-1β inhibitor from 1997 to 2021.

Figure 2

General analysis based on countries. A. Total publication of Top 10 countries with the most publications. B. Total citations of Top 10 countries with the most citations. C. Network of countries represents co-authorship analysis of countries. The link between two nodes stands for cooperation. The bigger size of nodes indicated the more cooperative studies. Colors showed the different times of the collaborations. D. Total link strength of Top 10 countries with the most cooperative studies.

Figure 3

General analysis based on institutions. A. Total publication of Top 10 institutions with the most publications. B. Network of institutions represent Co-authorship analysis of institutions. The link between two nodes stands for cooperation. The bigger size of the nodes indicated the more cooperative studies. C. Total link strength of Top 10 institutions with the most cooperative studies.

A

B

C

Figure 4

General analysis of journals. A. Top 10 journals with the most publications. B. Top 10 journals with the most local citation time. C. Co-citation analysis of journals. The link between two nodes stands for Co-citation. The bigger size of the nodes indicated the more Co-citation.

A

B

Figure 5

General analysis of manuscripts. A. Co-citation analysis of manuscripts. The size of the node represents the Co-citation of the manuscript. B. Co-occurrence analysis of keywords of manuscripts. Different colors represent different years.

Figure 7

General analysis of the trend of Anakinra. A. The number of publication articles of Anakinra from 1997 to 2020. B. Top 10 countries with the most publications and average article citations. C. Network of countries represents Co-authorship analysis of countries. The link between two nodes stands for cooperation. The bigger size of the nodes indicated the more cooperative studies. Colors showed the different times of the collaborations. D. Top 10 journals with the most publications. E. Co-citation

analysis of journals. The link between two nodes stands for Co-citation. The bigger size of the nodes indicated the more Co-citation. F. Co-occurrence analysis of keywords of manuscripts of Anakinra. Different colors represent different years. G. Top 10 authors with the most publications. H. Co-authorship analysis of authors. The link between two nodes stands for cooperation. The bigger size of nodes indicated the more cooperative studies. Colors showed the different time of the collaborations.

Figure 8

General analysis of the trend of Canakinumab. A. The number of publication articles of Canakinumab from 2009 to 2021. B. Top 10 countries with the most publications and average article citations. C. Network of countries represents Co-authorship analysis of countries. The link between two nodes stands for cooperation. The bigger size of nodes indicated the more cooperative studies. Colors showed the different times of the collaborations. D. Top 10 journals with the most publications. E. Co-citation analysis of journals. The link between two nodes stands for Co-citation. The bigger size of the nodes indicated more Co-citation. F. Co-occurrence analysis of keywords of manuscripts of Canakinumab. Different colors represent different years. G. Top 10 authors with the most publications. H. Co-authorship analysis of authors. The link between two nodes stands for cooperation. The bigger size of the nodes indicated the more cooperative studies. Colors showed the different time of the collaborations.

Figure 9

General analysis of the trend of Riloncept. A. The number of published articles of Riloncept from 2008 to 2020. B. Top 10 countries with the most publications and average article citations. C. Network of countries represents Co-authorship analysis of countries. The link between two nodes stands for cooperation. The bigger size of the nodes indicated the more cooperative studies. Colors showed the different times of the collaborations. D. Top 10 journals with the most publications. E. Co-occurrence

analysis of keywords of manuscripts of Rilonaccept. Different colors represent different years. F. Top 10 authors with the most publications. G. Top 10 authors with the total local citations.