

Title:

Prevalence, safety and long-term retention rates of biologics in Hong Kong from 2001-2015

Running head:

Long-term biologics utilization in Hong Kong

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Abstract

Background: Biologic agents were initially introduced as treatment for rheumatoid arthritis (RA) but have since been used for other medical conditions. As new biologics become increasingly widespread in treatment regimens, it is important to understand their safety and utilization in the post-marketing context.

Purpose: To investigate long-term prescribing patterns and the safety of biologics in real clinical settings in Hong Kong.

Methods: This was a population-based drug utilization study in Hong Kong using a territory-wide electronic medical database Clinical Data Analysis and Reporting System (CDARS). Patients who received biologic treatments from 2001 to 2015 were identified and their corresponding demographic and clinical details retrieved from CDARS. The annual prevalence of biologic prescriptions, the long-term retention rates and incidence rates of infections associated with biologic treatments were evaluated.

Results: A total of 30,298 patients (male: 44%) prescribed biologic treatments were identified from CDARS from 2001 to 2015. The annual prevalence of biologic prescriptions increased from 0.1 to 16.1 per 100 persons for both sexes. Infliximab had the highest first year retention rate of 95.6% among all biologics and continuously attained the highest retention rate from second to fifth year. The overall incidence rate of serious infections was less than 5 per 100 person-years. Specifically, the incidence rate of tuberculosis, upper and lower respiratory infections and herpes zoster were 0.52, 3.24, 4.99 and 1.01 per 100 person-years respectively.

Conclusion: This population-based study revealed an increasing prevalence of biologic prescribing. Results from the study described the long-term retention rates and incidence rates of serious infections of biologic treatments for all indications, and confirmed the safety of biologic treatments. Since this study provides an overview of all biologic utilization, further studies on cost-effectiveness, safety and compliance of treatment in different patients group are still warranted.

Key points

- Territory-wide electronic health database revealed that biologic use in Hong Kong increased steadily from 2001 to 2015 and accelerated faster in females than males.
- As the first approved biologic in Hong Kong, infliximab had the highest retention rate among all biologic treatments from first to fifth year.

- The overall incidence rate of serious infections in biologic users was less than 5 per 100 person-years, which addresses the safety concerns of biologic treatments.

1. Introduction:

According to U.S. FDA, biologics are broadly defined as biological products derived from human, animal, or microorganism using modern biotechnology.[1, 2] Since the late 1990s, advances in molecular biology have led to a variety of new biologics as alternative treatments for autoimmune diseases and cancer.[2, 3] Targets of biologics include various immune cells or cytokines that play a key role in local and systemic inflammation,[4] such as the tumor necrosis factor (TNF)-alpha, T-cells, B-cells, and interleukins (IL).[4] For biologics used in rheumatic diseases, anti-TNF biologics include both soluble receptors that serve as decoy receptors competing with TNF-receptors (etanercept) and monoclonal antibodies targeting the TNF-receptors (infliximab, adalimumab and golimumab).[4] Tocilizumab, on the other hand, is an IL-6 receptor inhibitor that binds specifically to IL-6 receptors.[5] Rituximab is a B-cell targeted monoclonal antibody acting against CD20.[4] Abatacept is a synthetic fusion protein that inhibits co-stimulation of T-cells.[4]

Biologics usage are expanding to indications beyond their original therapeutic targets. Many biologic agents were initially introduced as treatment for rheumatoid arthritis (RA) but were subsequently used for other conditions, such as psoriasis,[6] psoriatic arthritis,[7] ankylosing spondylitis,[8] and inflammatory bowel disease.[9] Monoclonal antibody ustekinumab is an antipsoriatic agent targeting IL-12/23, which also proved to be effective in patients with moderate-to-severe Crohn's disease.[10] Apart from autoimmune diseases, a combination of chemotherapy regimen and biologics such as aflibercept, bevacizumab, cetuximab, panitumumab and trastuzumab, are applied to advanced or metastatic cancer to prevent the proliferation of cancer cells or to slow tumor growth. [6, 7] Rituximab, for example, which is currently approved for the treatment of relapsed or refractory low-grade non-Hodgkin's lymphoma and is under investigation for the treatment of rheumatoid arthritis, is even more wide-ranging in terms of its potential expanded indication.

Moreover, biologics acting on different therapeutic targets can achieve other treatment goals. Antithymocyte and basiliximab are immunosuppressants introduced in renal transplant. [8] Ranibizumab, a recombinant humanized monoclonal antibody fragment, binds to vascular endothelial growth factor (VEGF) to treat age-related macular degeneration or diabetic macular edema.[9] Denosumab is a fully human monoclonal antibody which specifically targets the receptor activator of nuclear factor kappa B ligand (RANKL), and is used to treat osteoporosis and bone loss associated with metastases or giant cell tumor.[10] Palivizumab acts against the fusion protein in the respiratory syncytial virus (RSV).[11]

Due to the significant physiological role of biologics in host defense, an increased risk of infection is a key safety concern. Complications from a variety of infections were observed in patients using biologics, among which tuberculosis (TB) is most notable, followed by serious respiratory infections, soft tissue, and skin infections.[12, 13] Both severe and non-severe infections were reported in several observational studies, especially the increased risk of herpes zoster (HZ) associated with anti-TNF agents.[14-19] With an increasing number of new biologic options in treatment regimens, it is crucial that healthcare professionals are aware of the treatment patterns and safety of biologics.

This study aims to investigate the long-term use of biologics and examine the risk of infection associated with biologic prescriptions in patients in real clinical settings whilst bridging the research gap of biologic surveillance in Hong Kong, and to act as a reference for healthcare professionals globally.

2. Methods:

2.1 Data source

We identified patients from the Hong Kong Hospital Authority (HA) using the Clinical Data Analysis and Reporting System (CDARS). CDARS is a database developed by the HA, a statutory body which manages all public hospitals and their ambulatory clinics in Hong Kong. The service is available to over 7 million Hong Kong residents.[20] CDARS has been used for various high quality pharmacoepidemiological studies. [21-23] Patient specific data, which are recorded by trained clinicians, include basic demographic information, payment method, prescription information, pharmacy dispensing information, diagnosis, and admission and discharge information. CDARS contains the records of all in-patient, out-patient, and emergency room admissions in HA clinics and hospitals from 1995. Records are de-identified to protect patient confidentiality. A unique patient reference number is generated to facilitate data linkage and identification. Detailed descriptions of CDARS can be found in a previously published data study.[20]

2.2 Patient identification and the list of biologics in Hong Kong

This is a retrospective observational study of patients treated with biologics in Hong Kong. Patients who were prescribed any biologics in all public hospitals from January 1, 2001 to December 31, 2015 were identified from CDARS. We used the unique patient reference number to retrieve relevant records of these patients with demographics (age, sex), clinical diagnosis in International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and drug (name and dose) records.

There were 18 types of biologics available in the Hong Kong HA Drug Formulary 2014 (see Electronic Supplementary Material 1). According to the list, the common indications of biologics include autoimmune diseases (RA, psoriasis, osteoarthritis), osteoporosis, chronic renal failure, respiratory syncytial virus and various kinds of cancer. The list was reviewed by clinical pharmacists and pharmacoepidemiology researchers.

2.3 Prevalence of biologic use

The methodology for determining biologic use was based on that used by Man et al. in patients with methylphenidate and atomoxetine treatments.[24] The annual prevalence of prescribing was calculated by dividing the total number of all patients who received at least one biologic prescription in a year by the total mid-year population for that particular year. Population information was obtained from the Census and Statistics Department, The Government of the Hong Kong Special Administrative Region. Similar methodology had been used for other drug utilization study.[25] Associated diagnoses were identified as all diagnosis made on the biologic prescribing day, including autoimmune diseases, osteoporosis, cancer, and chronic renal failure and respiratory syncytial virus.

2.4 Long-term retention rates

The methodology was adapted from that used by Wong et al.[26-28] and Lhatoo et al.[29] in patients with chronic epilepsy in the UK. The retention rates for each biologic agent were estimated as the percentage of patients continuing on biologics at a specified period of time.[26, 27] Exposure duration started from the index date (the date of first biologic prescription) and ended at the right censor date (the date of discontinuation of treatment when a prescription was not filled within a grace period, treatment switching, the date of death or December 31, 2015, whichever came earlier). The grace period for each treatment was defined as the average treatment gap - the time (in days) between two consecutive prescriptions for the same biologic treatment. Patients were excluded from re-entering the cohort once their treatment was terminated.

2.5 Risk of infections

This study particularly focused on serious infections which are defined as those led to hospitalization. Infections discussed in this study include TB, upper and lower respiratory infections, and HZ infections, classified by ICD-9-CM respectively. The incidence rates of infections during the exposed time for each biologic treatment were calculated by dividing the number of corresponding infection cases by the patient-time of exposure. The exposed time has the same definition as the exposure duration stated in the previous section.

2.6 Statistical analyses

Microsoft Excel, GraphPad Prism v7.0 (GraphPad Software, CA, USA) and Statistical Analysis System (SAS) v9.4 (SAS Inc., NC, USA) were used for data manipulation and analysis.

3. Results

3.1 Prevalence of biologic use

We identified a total of 30,298 patients (44% male) from CDARS who were prescribed biologic treatments from 2001 to 2015. Overall, the annual prevalence increased from 0.1 to 16.1 per 100 persons from 2001 to 2015 (**Figure 1**). Although the uptake of biologics in patients with RA increased in both sexes, it accelerated faster in females than males from 2011. The increased trend of prevalence was found in both sexes while the prescribing prevalence in males (14.0 per 100 persons) was lower than females (17.9 per 100 persons). In the latest observation year of 2015, denosumab was the most common treatment that was prescribed to 2,581 patients, accounting for 22.5% of total patients prescribed biologics, followed by ranibizumab (2,009 patients), and trastuzumab (1,528 patients). Increased prescribing trends were observed for most of the biologic agents except for antithymocyte immunoglobulin.

Patient age and the diagnosis associated with biologic treatments are presented in **Table 1**. Generally, patients prescribed biologics presented with different types of autoimmune diseases, as well as osteoporosis, advanced cancers, and metastasis. Etanercept was the most common biologic treatment among patients with RA in 2015, contributing 28.7% of total use, followed by tocilizumab (25.5%), adalimumab (12.2%), and golimumab (11.6%). In general, the use of individual biologic treatment increased in patients with RA, with the exception of infliximab. The usage of infliximab decreased from 2009 onwards; although it was once the most common biologic treatment among patients with RA.

Among biologics used in malignant diseases, the prescribing prevalence of trastuzumab ranked first and increased steadily since 2005. Basiliximab was more popular than antithymocyte in terms of prescribing prevalence as both of them were indicated for renal transplant. The mean age at treatment time was higher for patients indicated with aflibercept, denosumab and ranibizumab.

3.2 Retention rate of biologic treatment

We have five years of retention rates for all 18 biologics (**Figure 2**). Infliximab had the highest first year retention rate, followed by ustekinumab and ranibizumab. Infliximab also attained the highest retention rate from second to fifth year. Denosumab had the lowest first,

third and fourth year retention rate among all. Aflibercept had the lowest second year retention rate and golimumab had the lowest fifth year retention rate.

Specifically, we listed out biologics used in rheumatic disease given its long-term use (*Figure 3*). The TNF inhibitors had higher first year retention rates than the others. The selective T-cell co-stimulation blocker abatacept had the lowest retention rate from first to fourth year and, again, golimumab had the lowest fifth year retention rate.

3.3 Risk of infections

The overall incidence rate of TB in biologic users was 0.52 per 100 person-years. The TNF inhibitors had lower incidence rates of TB, upper and lower respiratory infections and HZ infections than other anti-rheumatoid agents. Rituximab had the highest incidence rates of serious infections among the group (*Figure 4*).

For biologic treatments in malignant disease, basiliximab had the highest TB incidence rate of 3.6 per 100 person-years. Antithymocyte immunoglobulin ranked second in the incidence rate of TB at 1.71 per 100 person-year and ranked first in the incidence rate of upper and lower respiratory infections and HZ infection (*Figure 5*).

The incidence rate of TB and HZ infection in biologics used in other diseases was relatively lower than the other two groups, while palivizumab had the highest incidence rate of both upper and lower respiratory infections (*Figure 6*).

4. Discussion

It is widely acknowledged that the uptake of biologics is a classic model[30] of the “technology adoption life cycle” i.e. slow uptake at the beginning by early adopters (such as academic clinicians) followed by early majority (such as medical colleagues of academic clinicians) and the late majority (all other clinicians). To the best of our knowledge, this is the first comprehensive study to investigate the long-term prescribing trends of biologics in Hong Kong with the technology adoption life cycle. Generally, the use of biologics has increased steadily over the last 15 years, and the rate of increase is observed to be accelerating over recent years. There was rapid market access of new biologics to clinical practice during the study period, probably due to the changing therapeutic position of biologics from secondary treatment in RA to an earlier therapeutic option for severe RA and cancers.[31] The availability of biosimilar products drives down the cost of biologics, which may also account for the increasing utilization trend of various biologics. Results of this study also implied an increasing trend of biologic prescriptions in both sexes, however, the rate of increase was slower in men than women. One possible explanation could be that as autoimmune diseases accounts for majority of biologic indications, women are affected 2.5 times more frequently than men by rheumatoid diseases,[32], and there is an increasing trend of disease prevalence in the past decade.[33] Also, as mentioned previously, denosumab, indicated mainly for osteoporosis, was the most commonly prescribed biologic drug in 2015, and there has been a sharp increase in hip fractures in Hong Kong and a relatively higher prevalence of osteoporosis in females than males.[34] However, because the scope of this study includes all biologics from the public hospital formulary and all potential indications, as well as the nature of the cross-sectional study design, there is no simple we cannot offer a simple explanation for the correlation between higher prevalence of diseases and the faster rate of increase in biologic prescribing in women. Further investigation is required to explore the underlying reasons for this phenomenon.

We examined the retention rate for 18 different biologic treatments up to five years. Several previous studies reported greater retention rates for etanercept and adalimumab compared to infliximab.[35-37] However, we observed that infliximab had the highest retention rate among all biologics, controversially, infliximab was also associated with more cases of infections, especially upper respiratory infections, than etanercept or adalimumab. The uptake of innovative medicine is subject to many clinical, economic, and policy factors, as well as evidence availability from a variety of data sources. Infliximab was the first biologic to be

approved by the U.S. Food and Drug Administration in 1998, with most of the available data from observational studies. A cohort study demonstrated that up to 50% of patients who achieve remission on infliximab will eventually relapse if the drug is discontinued compared with 35% of those who continued therapy.[38] If there is positive patient response to infliximab, maintaining treatment was advised rather than switching to alternative biologics.[39] A further reason for the wider use of infliximab could be the preferential coverage of biologic therapies for RA under the Expensive Drug Support Scheme (EDSS) offered by the Hong Kong Arthritis and Rheumatism Foundation. According to EDSS, patients with arthritic conditions are eligible to apply to the scheme, and applicants using infliximab are permitted two free infusions from hospitals participating in the scheme. Despite alternative biologics being available under the scheme, patients not using infliximab are required to send receipts of purchase to the Foundation and await approval before proceeding. With regard to the biologics used in oncology; bevacizumab, cetuximab and trastuzumab had a retention rate of five years. However, it was uncommon for patients to use these biologics continuously within the oncology setting, for example, bevacizumab might be used for age-related macular degeneration. As the linkage of treatment with indication is limited in this study, we do not intend to indicate the retention rate of biologics used in oncology settings since they are used on a case-by-case practice within a relatively short period of time. On the other hand, the results presented in *Figure 2* are subject to the number of patients in the evaluated year, hence careful interpretation is recommended/advised.

To gain a better understanding of biologics usage in chronic settings rather than oncology settings given the reasons mentioned before, the anti-rheumatoid agents are listed specifically for their long-term use. We found TNF inhibitors had a lower risk of infections, which partially explains the relatively higher long-term retention rates, although the difference did not reach statistical significance. Etanercept was the most common biologic agent among patients with various rheumatic diseases, which was confirmed in the latest report by the Hong Kong Society of Rheumatology Biologics Registry published in May 2018[40]. However, the report suggested that infliximab was associated with the highest TB incidence, followed by etanercept and adalimumab, which is at variance from our finding. Other infections were not discussed specifically in the report. Notably, results from the current study and the report were not comparable given the different context of the targeted population. Moreover, we observed a lower risk of TB infection in TNF inhibitors, which could be explained by the international and local guidelines on the screening of active or latent TB before initiating TNF treatment.[41, 42] While our study looked into all possible medical conditions for biologic usage, including

cancer, osteoporosis, transplantation, and infections, the report targeted only biologics used in immune diseases.

There are limitations in this study. First, we examined the treatment discontinuation/retention rate that acted as a composite outcome of “lack of clinical response” and “intolerance of adverse event”. However, the clinical management data did not include reasons for prescription changes thus we were unable to ascertain the cause of this discontinuation. Second, although the retention rate obtained in this study provided long-term treatment patterns of biologics, compliance with the biologic treatment varied greatly among individual biologics. Currently, there is no standard guidance on a method to track persistence and compliance with the initial biologic treatment.[43] Nevertheless, compliance is not a major issue for most of the treatments because biologics are generally administered by intravenous injection or combined with chemotherapy in a hospital setting. Third, this study did not include data from private healthcare settings, which may lead to underestimation of the actual prevalence. However, the public sector is the main provider of specialist care in Hong Kong.[44] Consequently, we believe that the majority of patients receiving biologic treatments are included in this study, and our sample should be highly representative of the Hong Kong population. Lastly, this study was a descriptive study that aimed to describe the utilization of biologic treatments and the corresponding incidence of common infections. Regarding the heterogeneity of different biologic treatments in terms of indications and the characteristics of the patients receiving treatments, we did not overstate any conclusion on the associations between the use of biologics and the risk of infection but provided absolute estimates of the incidence for each treatment rather than comparisons. Further studies are warranted for the evaluation of safe biologics use in different patient groups.

5. Conclusion

This descriptive study examined the use of 18 biologics in Hong Kong over a period of 15 years. With an increasing prevalence of biologic prescribing, it is important to raise awareness of the effectiveness, compliance, and safety of the treatment. Results from this study described long-term use and the incidence rates of serious infections of biologic treatments for all potential indications. Future studies are recommended to further investigate the safety and compliance of biologics used in specific therapeutic areas.

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Compliance with ethical standards

Ethic statement

The study protocol was approved by the Hospital Authority Hong Kong West Cluster and University of Hong Kong Institutional Review Board (UW14-602).

Conflict of interest

Xue Li has received research funding from the Food and Health Bureau of the Government of the Hong Kong. Kenneth Man received the CW Maplethorpe Fellowship and personal fees from IQVIA Holdings, Inc., unrelated to this work. Esther Chan has received research funding from Wellcome Trust, United Kingdom; National Natural Science Fund of China, China; The Hong Kong Research Grants Council, The Research Fund Secretariat of the Food and Health Bureau, Narcotics Division of the Security Bureau, of The Government of the Hong Kong Special Administrative Region; Bristol-Myers Squibb, Pfizer, Bayer and Janssen, a Division of Johnson & Johnson, for work unrelated to this study. Ian Wong has received grants from the Research Grants Council (RGC, Hong Kong), Innovative Medicines Initiative (IMI), Shire, Janssen-Cilag, Eli-Lily, Pfizer, Bayer, European Union FP7 program, outside the submitted work. Ian Wong is a member of the National Institute for Health and Clinical Excellence (NICE) ADHD Guideline Group, the British Association for Psychopharmacology ADHD guideline group, and advisor to Shire. Mengqin Ge and Celine Chui declare no conflict of interest.

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Tables

Table 1. Diagnosis associated with biologic prescriptions

	Mean age at treatment time (SD)	Autoimmune diseases				Osteoporosis	Cancer			Chronic renal failure	Respiratory syncytial virus	Others
		Rheumatoid arthritis	Joint pain	Psoriasis	Osteo-arthritis		Lymphoma	Leukemia	Chemo-therapy			
Abatacept (n=70)*	52.15 (12.58)	44	14	0	0	2	0	0	0	4	0	6
		62.9%	20.0%	0.0%	0.0%	2.9%	0.0%	0.0%	0.0%	5.7%	0.0%	8.6%
Adalimumab (n=485)	44.64 (14.51)	201	163	83	21	3	0	0	0	0	0	14
		41.4%	33.6%	17.1%	4.3%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	2.9%
Aflibercept (n=654)	70.21 (12.21)	2	39	0	14	8	1	0	64	18	0	478
		0.3%	6.3%	0.0%	2.2%	1.3%	0.2%	0.0%	10.3%	2.9%	0.0%	76.6%
Antithymocyte (n=696)	27.48 (20.26)	0	38	0	0	2	97	238	262	19	29	11
		0.0%	5.5%	0.0%	0.0%	0.3%	13.9%	34.2%	37.6%	2.7%	4.2%	1.6%
Basiliximab (n=1164)	45.96 (16.49)	39	199	36	12	34	59	35	243	408	14	85
		3.4%	17.1%	3.1%	1.0%	2.9%	5.1%	3.0%	20.9%	35.1%	1.2%	7.3%
Bevacizumab (n=2382)	57.89 (12.17)	7	96	2	19	9	31	5	2046	21	1	145
		0.3%	4.0%	0.1%	0.8%	0.4%	1.3%	0.2%	85.9%	0.9%	0.0%	6.1%
Cetuximab (n=2437)	61.56 (11.94)	7	120	2	11	8	78	2	2054	69	1	85
		0.3%	4.9%	0.1%	0.5%	0.3%	3.2%	0.1%	84.3%	2.8%	0.0%	3.5%
Denosumab (n=2965)	70.11 (14.67)	96	110	4	18	1511	11	0	1115	35	6	59
		3.2%	3.7%	0.1%	0.6%	51.0%	0.4%	0.0%	37.6%	1.2%	0.2%	2.0%
Etanercept (n=957)	44.85 (15.78)	509	206	115	47	7	6	0	6	7	0	54
		53.2%	21.5%	12.0%	4.9%	0.7%	0.6%	0.0%	0.6%	0.7%	0.0%	5.6%
Golimumab (n=391)	46.33 (14.3)	138	180	47	10	5	0	0	0	0	0	11
		35.3%	46.0%	12.0%	2.6%	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	2.8%

Table 1. Diagnosis associated with biologic prescriptions (continued)

	Mean age at treatment time (SD)	Autoimmune diseases				Osteoporosis	Cancer			Chronic renal failure	Respiratory syncytial virus	Others
		Rheumatoid arthritis	Joint pain	Psoriasis	Osteo-arthritis		Lymphoma	Leukemia	Chemo-therapy			
Infliximab (n=815)	42.43 (15.96)	494 60.6%	143 17.5%	67 8.2%	34 4.2%	31 3.8%	7 0.9%	0 0.0%	18 2.2%	15 1.8%	2 0.2%	4 0.5%
Palivizumab (n=236)	0.79 (4.39)	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	5 2.1%	2 0.8%	2 0.8%	7 3.0%	31 13.1%	189 80.1%
Panitumumab (n=75)	60.94 (11.72)	1 1.3%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	73 97.3%	1 1.3%	0 0.0%	0 0.0%
Ranibizumab (n=2523)	69.74 (13.61)	27 1.1%	572 22.7%	12 0.5%	114 4.5%	79 3.1%	131 5.2%	21 0.8%	237 9.4%	445 17.6%	5 0.2%	880 34.9%
Rituximab (n=6735)	59.67 (16.15)	75 1.1%	73 1.1%	21 0.3%	57 0.8%	0 0.0%	4355 64.7%	337 5.0%	1680 24.9%	124 1.8%	13 0.2%	0 0.0%
Tocilizumab (n=232)	50.89 (16.49)	187 80.6%	11 4.7%	2 0.9%	9 3.9%	0 0.0%	7 3.0%	0 0.0%	5 2.2%	2 0.9%	2 0.9%	7 3.0%
Trastuzumab (n=4612)	52.96 (9.69)	22 0.5%	9 0.2%	6 0.1%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	4394 95.3%	178 3.9%	3 0.1%	0 0.0%
Ustekinumab (n=15)	43.1 (11.38)	0 0.0%	3 20.0%	12 80.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%

* Total number of patients prescribed with certain biologics for all possible indications. Patients may have more than one diagnosis or be subject to more than one biologic. The others included any other diagnosis on the same biologic prescribing day.

Figure legends

Figure 1. Prevalence of biologic agents prescribing in Hong Kong from 2001 to 2015.

Figure 2. Five years of retention rates for all biologics.

Figure 2a - e represents the first, second, third, fourth, and fifth year of retention rate for all biologics included in the study. Values were expressed with 95% confidence interval.

Figure 3. Retention rates of biologics used in rheumatic disease.

Figure 3a - e represents the first, second, third, fourth, and fifth year of retention rate for drugs used in rheumatic diseases respectively.

Figure 4. Incidence rates of infections in biologics used in rheumatic disease.

Figure 4a - d represents incidence rates of TB, upper and lower respiratory infections and HZ infections. Values were expressed as incidence per 100 person-years with 95% confidence interval.

Figure 5. Incidence rates of infections in biologics used in malignant disease.

Figure 5a - d represents incidence rates of TB, upper and lower respiratory infections and HZ infections. Values were expressed as incidence per 100 person-years with 95% confidence interval.

Figure 6. Incidence rates of infections in biologics used in other diseases.

Figure 6a - d represents incidence rates of TB, upper and lower respiratory infections and HZ infections. Values were expressed as incidence per 100 person-years with 95% confidence interval.

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