A systematic review of the factors associated with the initiation of biologicals in patients with rheumatological conditions

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ABSTRACT

Objectives Biologicals play a crucial role in managing some of the rheumatological diseases, thus it is important for clinicians, healthcare institutions and policy-makers to understand why biologicals are initiated or refused so as to make better decisions to improve patients' disease outcomes. Although there have been many studies investigating factors associated with the initiation of biologicals for patients with rheumatological conditions, there have been no systematic reviews that provide a comprehensive summary. We aim to provide a summary of factors associated with biologicals' initiation for patients with rheumatological conditions.

Methods We performed a literature search in PubMed, Embase and PsycINFO. We identified and screened studies according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Factors were presented according to patient, disease-related, therapy-related, healthcare team-related and system in-place factors.

Results A total 1755 articles were reviewed and 24 articles were found to be relevant to our objective. Forty four factors reviewed were placed into five main categories: patient factors (n=13); disease-related factors (n=11); therapy-related factors (n=7); healthcare team-related factors (n=4) and system in-place-related factors (n=9). The factors studied by the published papers found to be associated with decisions to initiate biologicals varied widely.

Conclusion Forty two factors of five different categories were found to be associated with biologicals' initiation for patients with rheumatological conditions. Clinicians need to be mindful of the complex nature of these factors to optimise therapy of patients with rheumatological conditions. Healthcare institutions and policy-makers ought to be aware of any potential barriers to successful biologicals' treatment and address them accordingly.

INTRODUCTION

There are more than 100 rheumatological conditions. Some are degenerative conditions such as osteoarthritis, others are inflammatory and autoimmune conditions that cause the immune system to attack joints and muscles. Examples of inflammatory and autoimmune rheumatological conditions are rheumatoid arthritis (RA) and spondyloarthritis (SpA), which is a group of diseases consisting of ankylosing spondylitis (AS), psoriatic arthritis (PsA) and inflammatory bowel disease- (IBD) associated arthritis.

The treatment of rheumatological diseases such as RA and SpA include pain medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids in some cases. Conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate are also used to treat RA. In recent years, there have been therapeutic advances that have resulted in the development of biologicals, such as tumour necrosis factor- α (TNF- α) antagonists infliximab and adalimumab. Biologicals are genetically-engineered protein drugs derived from human genes given parenterally and they have demonstrated effectiveness in the reduction of joint inflammation and radiographic damage, and therefore produce a positive clinical response.¹ Groups like the American College of Rheumatology (ACR), Assessment of SpondyloArthritis International Society (ASAS) and the European League Against Rheumatism (EULAR) have set guidelines on the initiation of biologicals for various rheumatological conditions. An example of a common factor between all three guidelines on biologicals' initiation is when there is high disease activity and poor prognostic factors (eg, elevated serum biomarkers) despite therapy with non-biological agents.²⁻⁴ Due to their high cost and side-effect profile, the use of biologicals are typically recommended after patients have failed the first-line therapy.⁵

The treat-to-target recommendations, formulated in 2010 (updated in 2014) for RA and in 2014 for SpA by an international task force, have provided a basis for the implementation of a strategic approach in line with EULAR towards the therapeutic goal of remission and low disease activity.⁶⁻⁸ Despite the implementation of guidelines and recommendations, there could still be other factors which may result in the initiation or restriction of biologicals' therapy. As biologicals have the ability to attain unprecedented outcomes in patients when prior therapy fails to achieve the target,⁹ it is essential that clinicians recognise factors in addition to the approved indications in order to achieve optimal therapy for patients. Healthcare organisations and policy-makers also ought to be aware of any potential barriers to successful biologicals' treatment and address them accordingly.

Although there were many studies investigating factors associated with the initiation of biologicals for patients with rheumatological conditions, there have been no systematic reviews that provide a comprehensive summary in this area. Hence, we aimed to provide a summary of factors associated

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with biologicals' initiation for patients with rheumatological conditions by systematically reviewing the current literature. We hope that this systematic review will not only allow clinicians to be more aware of these factors and aid them in making clinical decisions, but also to bring awareness to healthcare organisations and policy-makers to address any potential barriers to biologicals' treatment.

METHODS

Our search protocol was consistent with the PRISMA statement¹⁰ (Preferred Reporting Items for Systematic Reviews and Meta-Analyses – www.prisma-statement.org).

Search strategy

Articles were extracted from databases PubMed, PsycINFO and Embase. The literature review started in July 2016 was current as of August 2016. The keywords used were (Biologics OR (Biological Therapies) OR (Biologic DMARDs) OR (Biologic agents) OR bDMARDs OR (Anti-TNF)) AND (Factors OR Causes OR Considerations OR Predictors) AND (Initiation OR Start) AND (rheumato* OR (ankylosing spondylitis) OR spondyloarth* OR (Psoriatic arthritis) OR (Inflammatory bowel disease-related arthritis)). The full search strategy is reported in (online supplementary file 1).

Study selection

The inclusion criteria of the studies were all peer-reviewed studies that explored decisions to initiate biologicals, and studies that look at factors that are associated with biologicals' initiation for patients with any rheumatological conditions. The exclusion criteria included case reports, case series and studies that are non-English. The selection was completed in two steps. Titles and abstracts were assessed systematically by two authors separately (WY and YH), considering the eligibility criteria. If there was lack of information from the titles and abstracts, full texts were obtained and assessed. Then, all full texts of the eligible studies were downloaded and read to verify the presence of every inclusion criteria. Hand searches were also carried out using the references of related articles. To assess the quality of both the quantitative and qualitative articles, QualSyst, a systematic review tool, was used.¹¹ A score was calculated for each article (0%–100%), with a higher score indicating higher quality of article. A conservative cut-off point of 75%¹¹ was used to determine article inclusion. Any disagreements arising from the study selection process was resolved through discussion between the two authors (WY and YH).

Data collection process

The following data were extracted independently by two authors (WY and YH) and were compared and checked for consistency: the names of the authors; the article's country of origin; the type of study; the sample size of each study; the method for data collection; the disease population studied; the factors studied that were found to be associated/not associated with biologicals' initiation; the limitations of the study; and the conclusion. Factors investigated were then classified into five natural categories adapted from WHO classification of factors affecting medication adherence:¹² patient factors; disease-related factors; therapy-related factors; healthcare team-related factors; and system in-place-related factors. The factors studied, types of studies and number of studies that investigated the factors and their conclusions (whether factors were positively associated with biologicals' initiation, negatively associated with biologicals'

initiation or were not found to have an association with biologicals' initiation) were presented accordingly. An illustration was proposed to aid understanding of the intricate factors that were associated with biologicals' initiation for patients with rheumatological conditions.

Statistical analysis

A binomial probability test was performed for each factor to find out whether the most frequently identified type of association with biologicals' initiation was significantly different from 50%. Factors with a p-value less than 0.05 means that the most common type of association reported differs significantly from 50% and hence the majority is significantly greater than 50%. If there was a tie, then we would be assessing the more frequently identified type of association and testing whether its corresponding percentage was significantly different from 50%.

RESULTS

As shown in (online supplementary figure 1), 1755 articles were retrieved by our searches with 1283, 28 and 444 articles gathered from PubMed, PsycINFO and Embase respectively. Hand searches were also carried out using the references of related articles where three extra articles were shortlisted. Out of the total of 40 articles that were shortlisted based on their titles and abstracts, 14 duplicates were removed and two articles were found to not fulfil the inclusion criteria on assessing all the full texts, leaving 24 articles for review. All 24 articles attained the relative conservative cut-off point of 75% for article inclusion.¹¹ In these 24 articles, 15 (62.5%) were cohort studies, 7 (29.2%) were cross-sectional studies and there were two (8.3%) qualitative studies.

The titles, authors, country of origin, research objectives, sample size and disease involved as well as the QualSyst score of the selected articles are presented in supplementary table 1. In these 24 articles, 19 (79.1%) articles involved patients with RA, three (12.5%) articles involved patients with AS, one (4.2%) article involved patients with both RA and SpA and one (4.2%) article involved patients with early inflammatory polyarthritis. Articles that are duplicated or do not fulfil the inclusion criteria are also presented in (online supplementary table 1).

A total of forty two factors were identified in the systematic review.

Patient factors

On reviewing a total of 13 studies found from searches, 13 factors were identified. As shown in [table 1](#), they were grouped into the following three categories: demographics, behaviour and others.

In general, younger age,^{13–22} male,^{18 22} race/ethnicity (Hispanics),^{17 23} occupation requiring physical work,¹⁴ higher education level,^{20 22} higher household income,^{17 20} being married/having a partner,¹⁷ patient's preference for biologicals¹³ and lower household healthcare financial burden²⁴ are factors that were positively associated with biologicals' initiation. There were factors with differing results, such as male^{15 20} and race/ethnicity,^{15 20 25} where some studies suggested that they were negatively associated or have no associations with biologicals' initiations.

Disease-related factors

A total of 11 disease-related factors from 14 studies were identified and are shown in [table 2](#). They were: higher disease activity;^{13 16 26–31} radiographic progression;^{13 27 30} greater disability

Table 1 Patient factors' association with initiation of biologicals for patients with rheumatological conditions

Factors	No. of studies which concluded that factor was positively associated with initiation	Types of studies	Ref	No. of studies which concluded that factor was negatively associated with initiation	Type of studies	Ref	No. of studies which concluded that factor was not found to be associated with initiation	Types of studies	Ref	P values
Demographics										
Younger age	10	C, QL, CS	13–22				1	C	48	0.01
Male	2	C, CS	18 22	1	C	20	2	C	15	1.00
Race/ethnicity (Hispanics)	2	C	17 23				3	CS, C	15 20 25	1.00
Race/ethnicity (African-Americans)				1	C	23	3	CS, C	15 20 25	0.63
Race/ethnicity (White)							2	C	20 25	0.50
Occupation requiring physical work	1	QL	14							1.00
Higher education level	2	C	20 22							0.50
Employment status							1	C	20	1.00
Higher household income	2	C	17 20							0.50
Married/have a partner	1	C	17							1.00
Behaviour										
Smoking				2	C, QL	13 14				0.50
Patient preference for biologicals	1	C	13							1.00
Others										
Lower household healthcare financial burden	1	C	24							1.00

C, cohort; CS, case control; QL, qualitative; Ref, reference

(HAQ) level;^{13 20 27} lower quality of life (SF36);¹³ anti-citrullinated protein antibody (ACPA) positivity;¹⁹ higher level of acute phase reactant;²⁷ younger age of onset of disease;^{32 33} contraindications to biologicals;¹³ more comorbidities;¹⁵ history of hospitalisation;¹⁸ and higher prevalence of sick leave.²⁷ All these factors were found to be positively associated with biologicals' initiation except contraindications to biologicals,¹³ which were suggested to have a negative association with biologicals' initiation. There were several factors with inconsistent associations, such as having higher disease activity¹⁴ and more comorbidities.^{16 18 20}

Therapy-related factors

Seven factors from nine studies were identified and these factors were further classified into three categories: drug, efficacy and regimen (table 3).

Methotrexate or leflunomide use (as compared with sulfasalazine or hydroxychloroquine)¹⁵ as well as non-biologic DMARD monotherapy (as compared with dual therapy),¹⁵ DMARD use,^{20 28} corticosteroid use,^{13 15 16 20 30} pain medication use,¹⁶ having poor response to ongoing treatment^{14 19} and patient's adherence to previous DMARDs¹⁵ were positively associated with biologicals' initiation.

Table 2 Disease-related factors' association with initiation of biologicals for patients with rheumatological conditions

Factors	No. of studies which concluded that factor was positively associated with initiation	Types of studies	Ref	No. of studies which concluded that factor was negatively associated with initiation	Type of studies	Ref	No. of studies which concluded that factor was not found to be associated with initiation	Types of studies	Ref	P values
Higher disease activity	9	C, CS	13 16 26–31				1	QL	14	0.02
Radiographic progression	3	C, CS	13 27 30							0.25
Greater disability (HAQ)	3	C, CS	13 20 27							0.25
Lower quality of life (SF36)	1	C	13							1.00
Anti-citrullinated protein antibody (ACPA) positivity	1	C	19							1.00
Higher level of acute phase reactant	1	CS	27							1.00
Younger age of onset of disease	2	C	32 33							0.50
Contraindications to biologicals				1	C	13				1.00
More comorbidities	1	C	15	2	C, CS	16 18	1	C	20	1.00
History of hospitalisation	1	CS	18							1.00
Higher prevalence of sick leave	1	CS	27							1.00

C, cohort; CS, cross-sectional; HAQ, health assessment questionnaire; Ref, reference; SF, short-form.

Table 3 Therapy-related factors' association with initiation of biologicals for patients with rheumatological conditions

Factors	No. of studies which concluded that factor was positively associated with initiation	Types of studies	Ref	No. of studies which concluded that factor was negatively associated with initiation	Types of studies	Ref	No. of studies which concluded that factor was not found to be associated with initiation	Types of studies	Ref	P values
Drug										
Type of non-biologic DMARD (methotrexate/leflunomide vs hydroxychloroquine and sulfasalazine))	2	C	¹⁵							0.50
Non-biologic DMARD monotherapy vs dual therapy	1	C	¹⁵							1.00
DMARD use	2	C, CS	^{20 28}							0.50
Corticosteroid use	5	C, CS, CC	^{13 15 16 20 30}							0.06
Pain medication use (NSAIDs, COX-2 inhibitors, acetaminophen)	1	C	¹⁶				2	C	^{15 20}	1.00
Efficacy										
Poor response to non-biologicals	2	QL, C	^{14 19}							0.50
Regimen										
Patients' adherence to previous DMARDs	1	C	¹⁵							1.00

C, cohort; COX-2, cyclooxygenase-2; CS, cross-sectional; DMARD, disease-modifying antirheumatic drugs; NSAID, nonsteroidal anti-inflammatory drug; QL, qualitative; Ref, reference.

Healthcare team-related factors

There were four healthcare team-related factors: physician's preference;^{14 28 34} care by a rheumatologist/internist;^{16 18} number of rheumatologist visit;¹⁷ and fewer number of medical visits pre-diagnosis of rheumatoid disease¹⁸ were found from seven studies and these are presented in [table 4](#). All factors were found to be positively associated with biologicals' initiation except for a number of medical visits pre-diagnosis of rheumatoid disease.

System in-place-related factors

Nine system in-place-related factors found from eight studies were also presented in [table 5](#). They were: greater countries' socioeconomic welfare;³⁵ lower level of restrictions in prescription of a first biologic;³⁵ increasing calendar year;^{18 20 22} higher subsidy;^{16 24} private insurance;^{16 28} geographic region of residence in the western United States;¹⁶ residence in rural environment;¹⁷ availability of federally qualified health centres near

place of residence;¹⁷ and geographic region of treatment centre in the United States.²⁰ All factors were found to be positively associated with biologicals' initiation except availability of federally qualified health centres near place of residence and the geographic region of treatment centre in the United States.

DISCUSSION

This is a systematic review that involved a comprehensive review of the literature involving factors associated with the initiation of biologicals for patients with rheumatological conditions. This review gives an overview of the type and number of studies which concluded that factors investigated were positively associated, negatively associated or were not associated with the initiation of biologicals.

This systematic review showed that there are many factors associated with biologicals' initiation in addition to the factors recommended in established guidelines. As illustrated in [figure 1](#),

Table 4 Healthcare team-related factors' association with initiation of biologicals for patients with rheumatological conditions

Factors	No. of studies which concluded that factor was positively associated with initiation	Types of studies	Ref	No. of studies which concluded that factor was negatively associated with initiation	Types of studies	Ref	No. of studies which concluded that factor was not found to be associated with initiation	Types of studies	Ref	P values
Physicians' preference for biologicals	3	QL, C, CS	^{14 28 34}							0.25
Care by a rheumatologist/internist	2	C, CS	^{16 18}				1	C	¹⁵	1.00
Higher number of rheumatologist visits	1	C	¹⁷							1.00
Fewer number of medical visits pre-diagnosis of rheumatoid disease							1	CS	¹⁸	1.00

C, cohort; CS, cross-sectional; QL, qualitative; Ref, reference.

Table 5 System in-place related factors' association with initiation of biologicals for patients with rheumatological conditions

Factors	No. of studies which concluded that factor was positively associated with initiation	Types of studies	Ref	No. of studies which concluded that factor was negatively associated with initiation	Types of studies	Ref	No. of studies which concluded that factor was not found to be associated with initiation	Types of studies	Ref	P values
Greater countries' socioeconomic welfare	1	CS	³⁵							1.00
Lower level of restrictions in prescription of a first biologicals	1	CS	³⁵							1.00
Increasing calendar year	3	CS, C	^{18 20 22}							0.25
Higher subsidy	2	C	^{16 24}							0.50
Private insurance	2	C, CS	^{16 28}							0.50
Geographic region of residence (western United States)	1	C	¹⁶							1.00
Residence in rural environment	1	C	¹⁷							1.00
Availability of federally qualified health centres near place of residence				1	C	¹⁷				1.00
Geographic region of treatment centre in the United States							1	C	²⁰	1.00

C, cohort; CS, cross-sectional; QL, qualitative; Ref, reference.

the decision involving the clinical initiation and administration of biologicals were dependent on five categories of factors. Clinicians should take these factors into consideration where appropriate so as to make clinically sound decisions for each individual patient who would present with a different mix of factors.

Given that some of the factors such as patient's preference for biologicals and disease activity may vary under different circumstances, a reassessment should be conducted at least yearly to assess his/her suitability for biologicals. This continuity of care is essential to improve patient's disease management and outcome.³⁶ In addition, there are some factors that can be modified and if they were addressed, it could lead to an increase in biologicals' initiation in clinically indicated patients. Examples of modifiable factors are improving follow-ups with rheumatologists and introducing policies to increase subsidies which could lead to an increase in biologicals' initiation. A study conducted in the United States found that having five or more rheumatologist visits in the year prior to the survey is a strong predictor of biologicals' initiation as compared with patients with one to four

rheumatologist visits.¹⁷ This highlights the importance of having affordable access to rheumatologists' care in initiating biologicals that can potentially improve patients' clinical outcomes.

Most studies which examined the association between disease activity and biologicals' initiation concluded that higher disease activity is positively associated with biologicals' initiation. This is in line with treatment algorithms in guidelines such as the ACR and EULAR which have recommended the initiation of biologicals when there is moderate to high disease activity, measured by validated instruments such as Disease Activity Score (DAS) 28 and Patient Activity Scale (PAS).^{2 3} Despite treatment algorithms in place, a qualitative study involving 10 Swedish rheumatologists making treatment decisions for hypothetical patients' cases concluded that DAS28 was not predictive of biologic prescription.¹⁴ However, this may not be indicative of actual clinical practice due to the study's small sample size, as well as simulation of cases with limited information provided. Radiographic progression,³⁷ greater disability (HAQ score),³⁸ lower quality of life (SF36 score),³⁹ positivity of anti-citrullinated protein antibody,⁴⁰ higher level of acute phase reactant,⁴¹ history of hospitalisation⁴² and higher prevalence of sick leave⁴³ are all indicators associated with higher disease activity. Thus it is no surprise that these factors were also found to be positively associated with biologicals' initiation. While these factors may not be indicated for biologicals' initiation in the guidelines, they could be useful factors for clinicians to take into account given their close links with disease activity. It is interesting to note that studies have different conclusions regarding how the number of comorbidities are associated with biologicals' initiation. The positive association of an increase in the number of comorbidities and biologicals' initiation may imply that patients with more comorbidities may seek aggressive treatments such as biologicals, whereas the negative association of an increase in the number of comorbidities and biologicals' initiation may imply that biologicals are contraindicated in many comorbid conditions, such as infections and heart failure.⁴⁴ Hence, the positive or negative association of the number of comorbidities with biologicals' initiation

Figure 1 Illustration of factors affecting initiation of biologicals in patients with rheumatological conditions.

depends on the relative roles patients and clinicians play during the treatment process.

While findings from the systematic review suggests that disease-related and therapy-related factors identified in the study generally did not deviate from existing ACR/ASAS/EULAR recommendations,²⁻⁴ there were also some interesting findings. For instance, two studies suggested that patients who had a younger age of onset of disease were more likely to be initiated on biologicals.^{32,33} Reasons for this finding could be further explored as it is not a factor mentioned in the existing guidelines. Further studies can be done in the future to find out if patients who had a younger age of disease onset could indeed have better benefit-risk profile from the initiation of biologicals as compared with patients who had the disease at an older age. In addition, a study also noted that better adherence to non-biological DMARD therapy is positively associated with biologicals' initiation.¹⁵ This may signify that patients with better adherence may be more motivated to seek additional treatment. There were also other patient-, healthcare team- and system in-place-related factors which were found to be associated with biologicals' initiation that were not mentioned in guidelines and recommendations. From the findings, patients with a higher household income and higher educational levels were associated with biologicals' initiation, indicating disparities in access to these agents that have been shown to be effective in treating many rheumatological conditions. Another study also observed that the probability of initiating biologic agents was lower among those living in areas with federally qualified health centres.¹⁷ This may indicate that such areas may have fewer medical care resources available due to the poverty of many of the residents in these areas. This observation may also suggest the difficulties primary care physicians face in gaining access to specialists for their patients,⁴⁵ which could be due to the lack of insurance and specialty care resources in these health centres. Hence, this systematic review can serve to complement existing guidelines so that clinicians as well as healthcare institutions and policy-makers can recognise factors that can potentially affect biologicals' initiation and address the factors by exploring the reasons behind these observations. This systematic review can also serve as a guide for future studies examining factors to initiate biologicals, especially for factors that were found to have conflicting results.

Some factors, such as younger age, male, race/ethnicity (Hispanics and African-Americans), higher disease activity, more comorbidities, pain medication use and care by a rheumatologist/internist, were found to yield contradictory results on further evaluation of this present systematic review. The reason could be that factors associated with the initiation of biologicals might be context-driven.³⁵ The different circumstances which the studies took place in, which may include different geographical locations, cultures, characteristics of patients involved and year in which the studies were conducted, could all interact to produce inconsistent outcomes. Therefore, when addressing these factors, clinicians should exercise clinical judgement within the context when providing medical care to patients.

A point to note is that the articles which were included in this systematic review did not differentiate between the initiation of biologicals and generic versions of biologicals, which are referred to as biosimilars. Like generic pharmaceuticals, biosimilars may face lower cost and require less time to obtain approval. In Europe, studies suggest that biosimilars often are priced about 25% lower than biologicals⁴⁶ and they are

currently on the rise as patents for many biologicals will soon expire. Thus, the factors affecting the initiation of biosimilars may differ from the ones seen in this systematic review. They could potentially be more focused on physician's preference and regulatory issues rather than socioeconomic factors.

This systematic review has adopted a search of multiple databases, namely PubMed, PsycINFO and Embase, which ensure that more articles were included, to yield a more comprehensive and complete systematic review.⁴⁷ Nonetheless, we acknowledge that despite a search on multiple databases, there could still be incomplete retrieval of articles. The PRISMA guidelines were followed so as to ensure transparency in the articles' selection process and clarity in reporting.

As the present study is a systematic review and not a meta-analysis of the effects of various factors on initiating biologicals, we do not know the aggregate magnitude of each factor. However, this systematic review has summarised the literature as much as possible, and has presented the factors clearly into five major categories to allow clinicians, healthcare organisations and policy-makers to have a holistic overview of the factors that could be associated with the decision to initiate biologicals' therapy. Of note, as the studies reviewed in this systematic review were carried out in different countries where there may be difference in health systems, funding of medications, demographics and culture, it is difficult to conclude the magnitude of each factor. The lack of consensus in factors associated with biologicals' initiation also proved that the context matters. As most studies were conducted in Western countries in North America and Europe, countries in Asia and Africa might need to stipulate and impose their own set of factors when making decisions on biologicals' initiation, using this systematic review as a general overview. It should also be noted that an overwhelming majority of the studies in this systematic review involved patients with RA. There were only a few articles involving patients with SpA. Thus, when treating patients with SpA, clinicians may have to exercise more caution, as not all of the factors investigated in this systematic review apply to these patients.

CONCLUSION

In conclusion, forty two factors of five categories were found to be associated with the initiation of biologicals for patients with rheumatological conditions. Clinicians, healthcare organisations and policy-makers should recognise these potential factors and make efforts to achieve optimal therapy for patients through medication evaluation and disease monitoring programmes as well as improvement in policies.

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