Peer Review File

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Comment 1: This paper was innovative and takes great care to measure an often overlooked subject. My comments mainly centre around adding more RA specific content and patient level implications. Overall this paper summarized a complicated topic and presented the data in a high-quality format.

Reply 1: We sincerely thank the reviewer for the comments.

Comment 2: Line 55-56 Unclear what this sentence means. What is "compare markers between studies"?

Reply 2: We sincerely thank the reviewer for the comments. As there is no consensus in the literature on the stages and markers of translational research, studies often use different markers to estimate lag times. This makes it difficult to directly compare the results. We've made a small change in the text to improve comprehension.

Changes in the text: We have changed the term "compare markers between studies" to "compare with other studies" (see line 59).

Comment 3: Line 46-47 Unclear language, event dates of what? Please specify.

Reply 3: We have modified our text as advised.

Changes in the text: We specify by changing the text to: "The dates of translational research activities were identified from markers and steps". (see lines 47-48).

Comment 4: Line 86 Could go further here, is also associated with worse patient reported outcomes, higher direct and indirect cost, worse long term outcomes, more erosive joint damage.

Reply 4: We sincerely appreciate the reviewer for the comments. We have added the impacts of late treatment and updated references.

Changes in the text: We have modified our text as advised (see lines 92-96): Clinical guidelines recommend early diagnosis and treatment (13–15) as delayed disease management is associated with the worsening of the clinical condition, including pain and loss of quality of life, more erosive joint damage, extra-articular manifestations and increased morbidity and mortality (16–19). In addition, treatment delays are related to

higher direct and indirect costs of disease management, as patients fail to achieve better outcomes and negatively impact health systems(11,20).

Comment 5: Line 97: I think that some key messaging is missing here with respect to the disease progression and the reasons for the importance of measuring time to translation of new biologics.

The treatment algorithm in RA is to prescribe an initial csDMARD or combination of csDMARDS, then if inadequate to control inflammation move to a biologic bDMARD or a combination of a biologic and 1 or more csDMARDs. As drugs have primary or secondary failures, physicians will then switch medications to another biologic or combination of biologic and csDMARD. Since only one biologic can be prescribed at a time, and since biologics cannot be re-prescribed after failure, and since different patients have different responses to each biologic, there is a persistent need for new biological medications in the marketplace to give physicians additional options to switch patients to. More treatment options mean that sub-optimal therapies can be switched for different potentially more effective therapies.

Therefore, the impact of wait times for new biologics in clinical practice is the possible denying a patient switch from a less effective treatment path to a more effective treatment path.

Reply 5: We appreciate your valuable comments. We have modified our text as advised.

Changes in the text: We have inserted some key messages relating to disease progression due to translation gap of new biological (see lines 108-112): Considering that patients may experience failures to control the disease, it is relevant that physicians and patients have more medicines available promptly to contain the progression of the disease. This could minimize the time lag for switching drugs that have failed to control the disease for others that can provide personalized treatment, with better outcomes.

Comment 6: Line 359: Would be good to see an implication for rheumatology clinical practice on the benefits of faster translation of bdmards to clinical practice.

Again, implications could be more treatment options for clinicians, better options for patients etc.

Could you please share some RA specific treatment benefits.

Reply 6: We sincerely appreciate the reviewer for the comments. We have added some benefits of faster translation in the clinical practice.

Changes in the text: We have modified our text as advised (see lines 404-408): Specifically in the clinical practice, the benefits of faster translation of new biological drugs can expand therapeutic options for managing the disease on time. With this, patients could have better results and quality of life, such as control of erosive joint damage and fewer extra-articular complications.

Comment 7: In your discussion you could contrast the average time it takes to switch a biologic (1-3 years in most studies) and the time it takes to approve and use a new biologic. Something that connects the RA specific implications with the overall implications.

Reply 7: We sincerely appreciate the reviewer for the comments. We understand that this discussion would be a limitation of the study.

Changes in the text: We have added the following text (see lines 390-393): In addition, the average time it takes to switch from one biological to another is also not included in the time interval estimated in this study. When few treatment alternatives are available, patients may experience a longer delay when they need to access other DMARDs.

Comment 8: Figure 1: In the legend, consider adding what T1, T2, T3 labels correspond to.

Reply 8: We appreciate your valuable comments. We understand that it is necessary to insert the legend for better understanding of the figure.

Changes in the text: We have included the legend (lines 637-639): Stage 1 (T1) has as initial and final markers the publication of the first clinical trial of phase 1 and the registration by Anvisa, respectively. Stage 2 (T2) starts from the first systematic review until the publication of the practice guideline; stage 3 (T3), from the medicines acquisition to its dispensation in the SUS.