A New Hope for Delaying Clinical Onset of Rheumatoid Arthritis: Early Intervention with Rituximab

ARTICLE INFORMATION

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ABSTRACT

Rheumatoid arthritis (RA) is a highly prevalent autoimmune disease that affects 16 million people globally. It is caused by an inflammatory autoimmune response that results in swelling of the joints and chronic pain. While we know that RA operates via the immune system, the specific mechanisms of RA pathogenesis are not fully understood, making diagnosis and treatment options limited. Rituximab, a monoclonal CD20 antibody, is a current form of RA treatment that specifically targets autoreactive B-cells to help mitigate the symptoms of RA at the clinical stage. Gerlag et al. (2019) outline a preventative window of opportunity for preclinical RA intervention with rituximab and identified two predictive biomarkers through exploratory methods. Their findings demonstrate that early administration of rituximab during preclinical RA delays disease onset and impedes its progression. This timeframe for intervention offers a promising first step for future studies investigating RA mechanisms and early treatments.

Keywords: Rheumatoid arthritis, rituximab, B-cell directed therapy, preclinical intervention

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Arthritis is currently a prevalent chronic health condition amongst Canadians, which results in reduced quality of life and loss of productivity.[1,2] Autoantibody positive rheumatoid arthritis (RA) is a common form of arthritis that affects over 16 million people worldwide.[2] As an autoimmune disorder, RA develops as a consequence of autoantibody formation and is characterized by joint inflammation, stiffness, and damage, which leads to systemic chronic pain.[2] Although individuals can be diagnosed and treatment options are available to reduce symptoms, there is currently no known cure due to uncertainty surrounding the biological mechanisms that underpin the disease.[3,4] Additionally, it is difficult to establish a concrete timeline for how RA develops since disease onset and progression varies between individuals due to its complex pathogenesis.[3,4] However, intervention ahead of RA onset could thwart the disease altogether, suggesting a preventative window of opportunity for treatment.[5] Evaluating the effects of B-cell therapy on preclinical RA, the stage before arthritic development, is an opportune origin for exploratory research.[5] The preclinical phase entails the presence of RA biomarkers prior to the clinical manifestation of the disease. This presents an opportunity for earlier diagnosis and treatment and may allow for earlier applications of preventative measures. Inflammation in RA is associated with an immunological response. This response is partially mediated by antigen-presenting B-cells, their cytokines, and their associated antibodies.[6] B-cells can serve as efficient antigen-presenting cells, which activate T-cell responses, thus resulting in inflammation. B-cells also produce cytokines that enhance inflammatory responses. The antibodies produced by B-cells also trigger complementary activation, which further promotes inflammation, making B-cell receptors a key target in early diagnosis and potential treatment for RA within B-cell therapy.[7]

The antibody, rituximab, is an important factor when attempting to prevent the development of RA. Originally used to treat lymphoma, rituximab is a drug used in B-cell therapy. Rituximab works by initially binding to the CD20 receptor on a B-cell, prompting the cascade of numerous systems, including apoptosis and cytotoxicity (Figure 1).[8] This is effective for arthritis treatment, especially in the preclinical stage, as the specificity of antibodies allows for specific binding to CD20+ autoreactive B-cells.[8] After binding to the cells, rituximab induces antibody-mediated cytotoxicity, which involves the binding of an effector cell to the rituximab-CD20 complex, resulting in the lysis of the autoimmune B-cell.[8,9] The variability of these systems promotes the clinical efficacy of rituximab, which assists with the creation of novel treatment regimens.[9] The high prevalence and disease burden of RA drives the need for additional research, specifically with regards to rituximab-induced B-cell therapy, to mitigate RA's progression and prevent its onset.

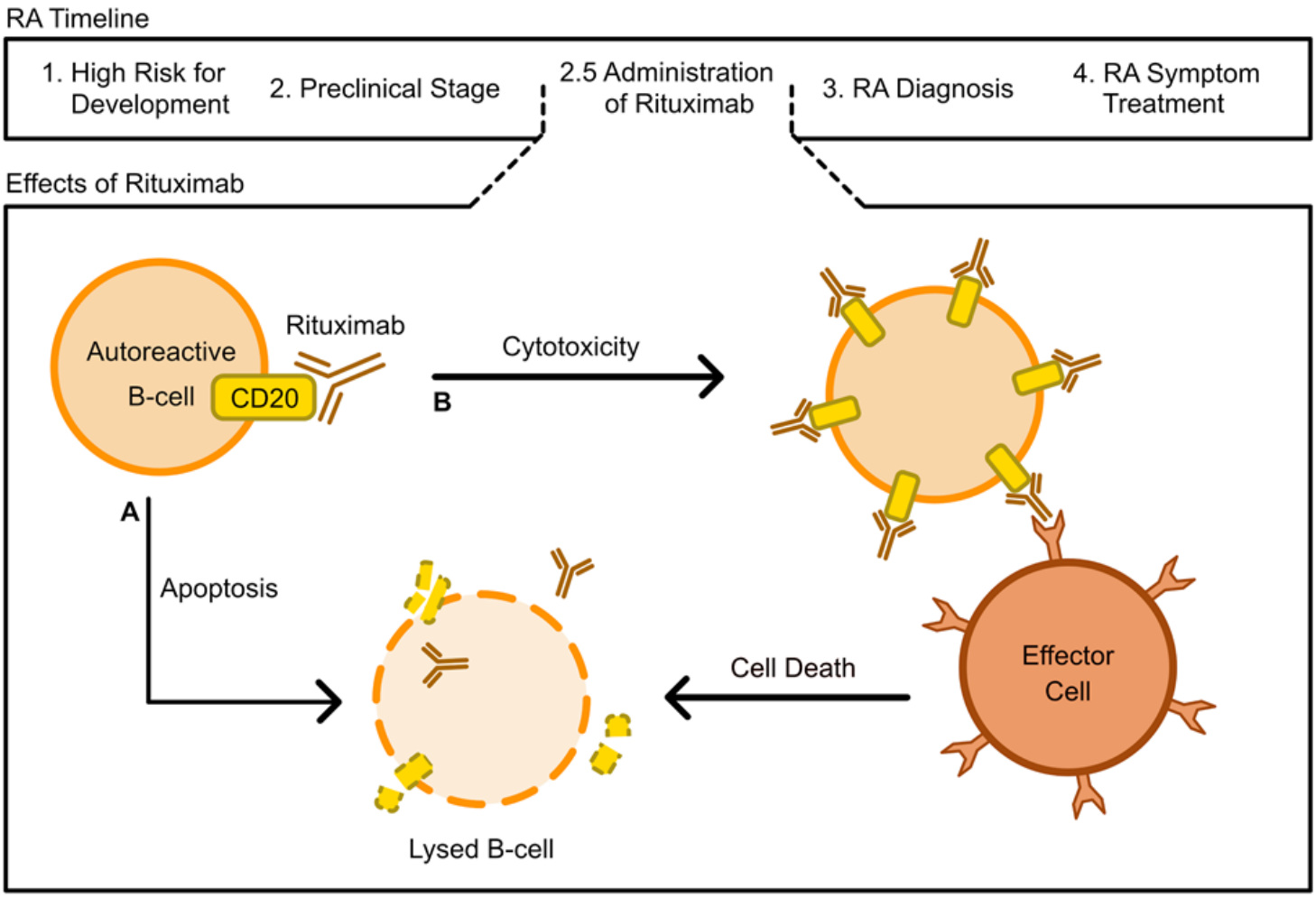

Figure 1. Illustration demonstrating the effects of rituximab in rituximab-induced B-cell therapy. Upon administration during the preventative window of opportunity, within the RA timeline, rituximab works to selectively target CD20 receptors on autoreactive B-cells. This results in either (**A**) apoptosis and death of the cell or (**B**) cytotoxicity. On pathway **B**, effector cells recognize rituximab and promote cell death, limiting the number of autoreactive cells in the body.[5,8,9]

A study by Gerlag et al. (2019) explored the effects of B-cell directed therapy using rituximab in individuals during the preclinical phase of RA.[5] 81 subjects were recruited based on the presence of biomarkers, such as rheumatoid factors (RF) and anti-citrullinated peptide antibodies (ACPA).[5] These risk factors indicate a 40% increase in the risk of RA development within two years.[5] Macrophages may be activated by RF and ACPA, resulting in increased cytokines and chemokines associated with the clinical manifestation of RA.[5] Of the 81 subjects, 41 received a single infusion of 1000 mg rituximab and 40 received a placebo.[5] Statistical analyses revealed a significant decrease in the number of B-cells within four weeks post-treatment, along with significant drops in multiple RFs.[5] Rituximab intervention reduced the risk of arthritis development by 55% at 12 months, and 53% at 18 months.[5] Although the effect of rituximab was statistically significant, its preventative effects decreased over time, showing temporary prevention.[5] Researchers suggest the clinical phase of RA can be avoided through repeated treatment with rituximab, supporting the idea of a preventative window of opportunity.[5]

Whether repeated treatment has this potential is an important research question with revolutionizing outcomes, but requires further investigation.

Through exploratory methods, the researchers also identified two biomarkers effective in predicting the onset of RA: erythrocyte sedimentation rate and anti-citrullinated α-enolase.[5] Considering the preventative window of opportunity, the integration of these predictors into the overall B-cell treatment regimen is important in successfully implementing the intervention prior to pathogenesis. This is why future research focused on increasing our knowledge of reliable diagnostic predictors is necessary to provide more effective RA treatment. It is also worth noting that patient heterogeneity and the complexity of RA itself can interfere with successfully determining at-risk individuals prior to pathogenesis. Therefore, being limited to only two predictors is insufficient. This emphasizes the necessity to discover additional predictors to broaden the extent to which at-risk individuals are identified.

Current treatments are only administered in RA patients after the clinical onset of the disease, but it is now possible to identify risk factors during earlier stages before RA onset.[5] Gerlag et al. (2019) demonstrate a potential preventative window of opportunity where early intervention would delay the development of clinical RA and allow for greater chances of disease remission.[5] The preventative window outlined in this study describes the optimal time to target and eliminate autoreactive B-cells. These targets provide opportunities to predict mechanisms of attack and whether the current state of autoimmune B-cells in a patient's body lead to RA. Identifying the disease pathways via autoimmune B-cells can identify the immunological malfunctions that contribute to RA pathogenesis. Despite the promising conclusions from this study, the chosen sample solely being from the Netherlands may impact the generalizability of the results, as there is uncertainty regarding the reproducibility of the results in other populations.[5] Nevertheless, the findings serve as a gateway for other autoimmune-related disorders, providing the option to detect and identify autoimmune disorders prior to the emergence of signs and symptoms. Moreover, this new understanding of the clinical manifestation of the disease, through B-cell autoreactivity, provides further insight into potential treatment.

RA is a debilitating condition that impacts millions of people globally, reducing their quality of life while imposing a large financial burden. Intricate pathogenesis involving autoimmune B-cells contributes to the difficulties of diagnosing the disease, with current treatments only being administered after clinical onset. Gerlag et al. (2019) outlined a preventative window of opportunity and found two predictive biomarkers.[5] They demonstrated that rituximab intervention within the preclinical phase, during the preventative window, can temporarily prolong RA development. The findings are vital as they suggest that repeated administration of the treatment might be able to permanently delay RA's clinical development, although future studies that test this hypothesis are needed.[5] This could have monumental implications, preventing the onset of RA in future populations.

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