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Rituximab as an effective and probably safe treatment for granulomatosis with polyangiitis (Wegener's Granulomatosis)

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Granulomatosis with polyangiitis (GPA), formerly known as Wegener's Granulomatosis (WG) is a potentially fatal systemic autoimmune disease, mainly affects small and medium-sized blood vessels. GPA is characterized by necrotizing granulomatous lesions of the respiratory tract, vasculitis, and glomerulonephritis, and it could develop in various organs, especially ear, nose and throat (ENT), lungs, and kidneys. Choosing an appropriate therapeutic option for these patients has remained challenging. Majority of conventional treatments are associated with severe side effects. During the recent years, several studies have been published regarding the efficacy of rituximab (RTX) as either induction or maintenance agent. It was shown that this new biologic drug could decrease the rate of relapse, associated with fewer side effects.

After GPA diagnosis, a two-stage treatment strategy, containing an induction phase and a less toxic immunosuppressive remission as the maintenance regimen is initiated. There are two main therapeutic compounds used in the induction phase of GPA, corticosteroids (CS) and cyclophosphamide (CYP). These agents have been shown effective, but not safe for patients. In addition to the frequently reported side effects, there are some less described long-term undesirable outcomes, such as disease damage and increased risk of malignancies as the results of treatment with high dose CS and repeated cycles of CYP, respectively [1,2]. However, RTX seems to be more effective and may be safer than the CYP, but not inferior to daily cyclophosphamide treatment for induction of remission [3]. Moreover, successfully treatment of complicated GPA cases with RTX, for example, a patient with renal granulomatous mass was reported [4]. In the maintenance phase, in addition to low dose CS and maintenance CYP, there are some frequently employed options, including azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), and leflunomide (LEF). It seems that besides AZA and MTX, no one could be reported as a superior agent in GPA patients [5]. Although there is no consensus regarding the prior option, LEF was superior to both AZA and MTX [6]. However, LEF was reported to be more effective than AZA and MTX, but less safe than MTX. There are some studies reporting that RTX is a significantly safer option than AZA for using in the maintenance phase [7,8]. In fact, RTX not only was associated with a lower number of major/minor relapse but also led to less mortality when compared to the AZA group. It is worthy to note that although this new treatment has been found as a promising treatment for GPA patients, some patients are still refractory to RTX.

Now the questions are why we do not use RTX instead CYP, what benefits CYP offers, and which could not be achieved by RTX therapy. Regarding efficacy, RTX is at least as effective as CYP and probably superior in relapsing disease and shows more desirable safety profile [3]. Choosing the best treatment for GPA patients must take quality of life into account. As it was previously mentioned, CYP related side effects could significantly decrease the quality of life in such patients. For example, infertility, malignancies, and US FDA pregnancy category D for CYP are considered as serious barriers, which could encourage us to replace it with RTX. In fact, the appearance of these conditions might make the even more complex disease. Thereby, safely treatment of patients is as important as effectively treating. We believe that now it is time to switch from conventional treatments to RTX. For the aim of achieving induction phase, employment of RTX concomitant with temporary high dose CS is recommended for newly diagnosed patients. It could induce a relatively long-lasting disease remission ($\geq$6 months) in the majority of patients, which is also followed by avoiding disease damage. Such patients could receive RTX every 6 months at the dose of 500–1000 mg, according to clinical judgments as maintenance therapy [8]. Regarding patients currently on conventional immunosuppression as maintenance therapy, such as AZA and MTX, discontinuing adjuvants after 6 weeks is recommended, as the effects of RTX begin about 6 weeks after the infusions. Regarding refractory cases, RTX plus CS could be assessed without additional conventional immunosuppression [9]. Additionally, repeated courses of RTX seem to be effective in patients who did not respond to the first course. It is worthy to note that before RTX administration patients must be monitored for acute and chronic infections with long-term latency and also screened for any significant cardiomyopathy and cardiac arrhythmia.

However, some issues related to RTX therapy in GPA patients have remained largely unknown. Firstly, there is no consensus regarding the optimum dose and intervals for RTX. It is plausible that different patients need different doses, according to underlying metabolisms and enzymes' activities. It was observed that orbital masses in GPA are associated with a lower treatment response rate [9]. This was suggested to be the result of slower metabolism and/or not easily spreading drugs to remote places such as the orbit surrounded by fibrous tissue [9]. Thus, a higher total dose (up to 2000 mg per cycle) and repeated

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courses of RTX is recommended for diffuse/severe GPA patients and non-responders to the first course, respectively. Regarding maintenance therapy, 500–1000 mg every 6 months is recommended. Secondly, it should be determined that whether receiving fixed-schedule of RTX or waiting for B cell repopulation and/or ANCA titer is beneficial for patients. Although recent evidence implied no statistically difference in the relapse rate between individually tailored and fixed-schedule RTX regimens [10], receiving a fixed 500 mg RTX infusion on days 14, then 6, 12 and 18 months after the first infusion seem to be associated with a lower risk of disease relapse. However, individually tailored-arm patients received fewer RTX infusions. Nevertheless, more studies are required to clarify. Lastly, long-term side effects of RTX in GPA patients need to be evaluated. Interestingly, in contrast to CYP, it was reported that RTX treatment is not associated with an increased malignancy risk compared with the general population in ANCA-associated vasculitis [11]. Taken together because of at least similar efficacy and safer profile, RTX can be recommended as an alternative to CYP for GPA patients. However, further studies to assess its safety profile are strongly recommended.

Conflict of interest

None.

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