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IM - COMMENTARY

Cryoglobulinemic vasculitis: having giant steps; but there are still unanswered questions

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Cryoglobulinemic vasculitis (CryoVas) is a systemic immune-complex vasculitis which can be a life-threatening condition. In their article recently published by Internal and Emergency Medicine, Vacchi C et al. reported the safety and effectiveness of biosimilar of Rituximab CT-P10 in the treatment of CryoVas [1]. For a better understanding of this article, an overarching look to the historical picture of CryoVas and details of the usage of biosimilars will be helpful.

Cryoprecipitate was first described in a multiple myeloma patient in 1933 [2]. In the paper of 1950′s, etiologies among 121 patients with cryoglobulinemia, were multiple myeloma ($n=14$), disseminated lupus ($n=6$), alcoholics ($n=23$), chronic hepatitis ($n=1$) and miscellaneous ($n=45$) [3]. Enormous improvements had been observed regarding etiopathogenesis and treatment modalities of this concept (Fig. 1) [4].

In a recent French cohort, 56.1% of patients with mixed cryoglobulinemia (MC) were HCV-related [5]. Others were autoimmune diseases, essential, hematological/neoplastic, and infections in decreasing order. Circulating cryoglobulins may be detected in approximately 40% of HCV-infected patients, asymptomatically. CryoVas occurs in a minority of cases (< 2%) with long-term HCV infection and older age [6].

HCV also infects immune cells including B-lymphocytes, macrophages, peripheral dendritic cells and monocytes. Trigger effect leads to permanent clones of B-lymphocytes producing oligoclonal or monoclonal IgM [6]. During this inflammatory cascade, increase in titres of Rheumatoid factor and formation of immune complexes by the monoclonal IgM itself, HCV, and anti-HCV polyclonal IgG antibodies are frequently observed. Based on these pathogenic principles, we can conclude, CryoVas as an immune-mediated process that becomes independent from the triggering virus [6].

Management of patients with CryoVas should be tailored based on distribution and severity of the disease. For the patients with non-severe problems, treatment of the main cause-antiviral therapy is sufficient [7].

Sustained virologic response (SVR) is the absence of virus in serum after the treatment, for which a combination of pegylated interferon (PEG-IFN) plus ribavirin resulted as 50–60% SVR [7]. In recent years, direct acting antivirals (simeprevir, sofosbuvir) became the standard of care with high (> 95%) SVR. These agents lead to significant decrease in the incidence of MC and CryoVas. Low-dose corticosteroids may be used for constitutional and musculoskeletal features in CryoVas [6, 7]. Antiviral treatment solely was not enough to treat severe patients (ie, glomerulonephritis, mononeuritis multiplex, extensive cutaneous ulcers). The conventional immunosuppressives along with corticosteroids have been used without evidence from randomized controlled trials [7]. However, the outcomes with these modalities were not satisfied.

Biologic agents are milestones of inflammatory rheumatic diseases including vasculitis. The efficacy of rituximab (RTX) for treatment of severe cryoglobulinemic vasculitis has been demonstrated in randomized controlled trials [8]. Currently, RTX is recommended to control disease with or without plasmapheresis. It is usually required before initiation of antiviral therapy [6, 7]. Moreover, efficacy of low-dose RTX (250 mg/m^2 two times one week apart) in HCV-related CryoVas was reported [8]. Comparison of these two dosing regimens is necessary to define optimum dosage of RTX. Other area which had scarce data is the place of RTX in non-HCV-related CryoVas.

The economic impact of biologic agents is expected to be huge day by day. A RTX-biosimilar, CT-P10 was approved in Europe with significant budget savings. With a changing

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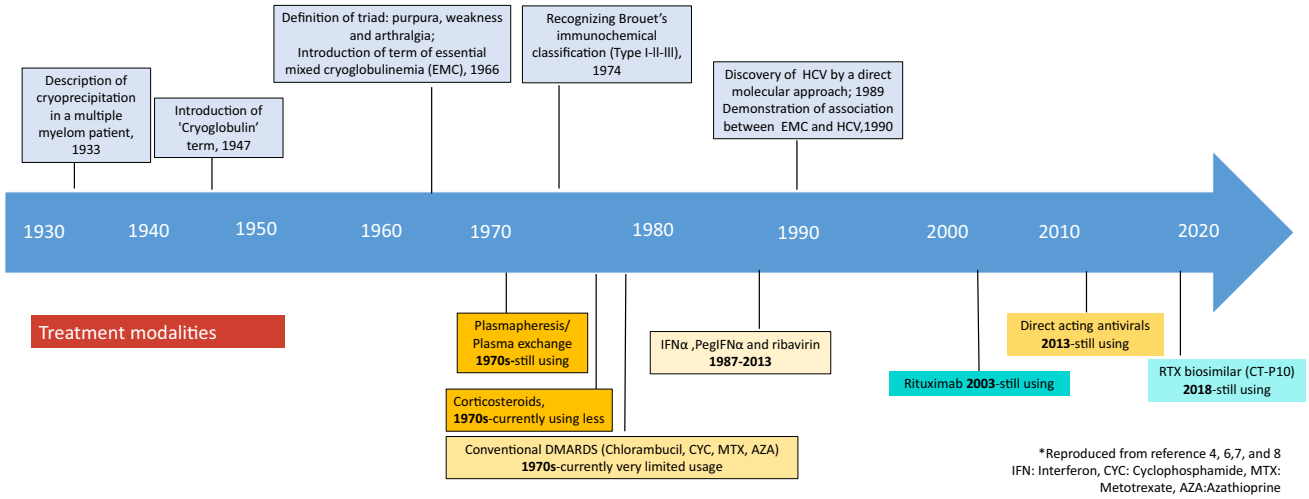

Fig. 1 Evolution and Milestones in Cryoglobulinemia and Cryoglobulinemic Vasculitis. Reproduced from reference [4, 6, 7], and [8]. *IFN* Interferon, *CYC* Cyclophosphamide, *MTX* Metotrexate, *AZA* Azathioprine

margin according to the model used, approximately 10% additional patients could be able to access RTX [9].

Park et al. showed the similarities of CT-P10 and RTX in terms of pharmacodynamics, immunogenicity, safety profiles among patients with rheumatoid arthritis (RA) [10]. In a very recent study, effectiveness of CT-P10 in scleroderma was also shown by an Italian multicenter study [11].

The answer of another burning question, was investigated by Shim et al. [12]. Switching from bio-originator RTX to CT-P10 in RA was well tolerated and did not result in any clinically meaningful differences regarding efficacy, pharmacodynamics, immunogenicity and safety.

The MARBLe study is the first study assessing CT-P10 in primary vasculitides [1]. The strengths of this study could be summarized as:

- Using two CT-P10 regimens (high dose and low dose)
- CT-P10 used as first line ($n=37$) and in patients switched ($n=14$)
- Including also non-HCV patients (49%)

There was no difference between patients treated with RTX and CT-P10 in term of clinical response; evaluated after 6 months of therapy. Moreover, CT-P10 firstly used and switched groups had similar positive findings. Two-thirds of study group were on low-dose CT-P10. Based on positive results of this study, a randomized controlled trial investigating effectiveness of this regimen will be rational.

Immune-mediated drug-related AE (IM-AE) including vasculitic re-exacerbation was also investigated. The onset of a new organ involvement or worsening of the autoimmune disease within 4 weeks following RTX was accepted as vasculitic re-exacerbation [13]. On the other hand, there are important differences between Group I and II in terms of disease duration, HCV positivity (51% vs.93%), skin involvement (80.4% vs. 68%), renal involvement (29.4% vs. 46.7%), RTX regimens, etc. It is very difficult to inference whether RTX bio-originator or CT-P10 had more immune-mediated drug-related AEs using data of this study due to many confounding parameters.

In conclusion, for the patients with HCV-related CryoVas, RTX, able to deplete CD19 positive-B cells, could also contribute to viral eradication making its combination with DAAs particularly attractive in the treatment of HCV-related CryoVas [6]. As a RTX-biosimilar, CT-P10 can be an effective and safe agent for not only HCV-related CryoVas, but also non-HCV-related along with budget advantage. Physicians should be aware of nocebo effect; as negative outcome or failure of therapy resulting from a patient's negative expectations toward a new therapy or a change in therapy. While dealing with nocebo effect, patients should be sufficiently informed during switching period.

Compliance with ethical standard

Conflict of interest Omer Karadag has received research grants from Roche, Pfizer as study investigator and received consulting fees from Abbvie, Abdi Ibrahim, Amgen, Celltrion, Janssen, Roche, UCB-Pharma. Emine Duran declared no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any type of authors.

Informed consent Fort his study formal consent is not required.

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