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[Intervention Review]

Treatment for hepatitis C virus-associated mixed cryoglobulinaemia

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ABSTRACT

Background

Hepatitis C virus (HCV)-associated mixed cryoglobulinaemia is the manifestation of an inflammation of small and medium-sized vessels produced by a pathogenic IgM with rheumatoid factor activity generated by an expansion of B-cells. The immune complexes formed precipitate mainly in the skin, joints, kidneys or peripheral nerve fibres. Current therapeutic approaches are aimed at elimination of HCV infection, removal of cryoglobulins and also of the B-cell clonal expansions. The optimal treatment for it has not been established.

Objectives

This review aims to look at the benefits and harms of the currently available treatment options to treat the HCV-associated mixed cryoglobulinaemia with active manifestations of vasculitis (cutaneous or glomerulonephritis).

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register to 30 November 2017 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and Clinical Trials.gov.

Selection criteria

All randomised controlled trials (RCTs) and quasi-RCTs looking at interventions directed at treatment of HCV-associated cryoglobulinaemic vasculitis (immunosuppressive medications and plasma exchange therapy) have been included.

Data collection and analysis

Two authors independently assessed the retrieved titles and abstracts. Authors of included studies were contacted to obtain missing information. Statistical analyses were performed using random effects models and results expressed as risk ratio (RR) or mean difference (MD) with 95% confidence interval (CI). The planned primary outcomes were kidney disease, skin vasculitis, musculoskeletal symptoms, peripheral joint arthralgia, peripheral neuropathies, liver involvement, interstitial lung involvement, widespread vasculitis and death. Other planned outcomes were: therapy duration, laboratory findings, adverse effects, antiviral therapy failure, B-cell lymphoma, endocrine disorders and costs of treatment.

Main results

Ten studies were included in the review (394 participants). None of them evaluated direct-acting antivirals. Seven studies were singlecentre studies and three were multicentre. The duration of the studies varied from six to 36 months. The risk of bias was generally unclear or low. Three different interventions were examined: use of rituximab (3 studies, 118 participants); interferon (IFN) (IFN compared to other

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strategies (5 studies, 223 participants); six IFN months versus one year (1 study, 36 participants), and immunoadsorption apheresis versus only immunosuppressive therapy (1 study, 17 participants).

The use of rituximab may slightly improve skin vasculitis (2 studies, 78 participants: RR 0.57, 95% CI 0.28 to 1.16; moderate certainty evidence) and made little of no difference to kidney disease (moderate certainty evidence). In terms of laboratory data, the effect of rituximab was uncertain for cryocrit (MD -2.01%, 95% CI -10.29% to 6.27%, low certainty evidence) and HCV replication. Rituximab may slightly increase infusion reactions compared to immunosuppressive medication (3 studies, 118 participants: RR 4.33, 95%CI 0.76 to 24.75, moderate certainty evidence) however discontinuations of the treatment due to adverse reactions were similar (3 studies, 118 participants: RR 0.97, 95% CI 0.22 to 4.36, moderate certainty evidence).

Effects of IFN on clinical symptoms were evaluated only in narrative results. When laboratory parameters were assessed, IFN made little or no difference in levels of alanine transaminase (ALT) at six months (2 studies, 39 participants: MD -5.89 UI/L, 95%CI -55.77 to 43.99); rheumatoid factor activity at six months (1 study, 13 participants: MD 97.00 UI/mL, 95%CI -187.37 to 381.37), or C4 levels at 18 months (2 studies, 49 participants: MD -0.04 mg/dL, 95%CI -2.74 to 2.67). On the other hand, at 18 months IFN may probably decrease ALT (2 studies, 39 participants: MD -28.28 UI/L, 95%CI -48.03 to -8.54) and Ig M (-595.75 mg/dL, 95%CI -877.2 to -314.3), but all with low certainty evidence. One study reported infusion reactions may be higher in IFN group compared to immunosuppressive therapy (RR 27.82, 95%CI 1.72 to 449.18), and IFN may lead to higher discontinuations of the treatment due to adverse reactions (4 studies, 148 participants: RR 2.32, 95%CI 0.91 to 5.90) with low certainty evidence. Interferon therapy probably improved skin vasculitis (3 studies, 95 participants: RR 0.60, 95% CI 0.36 to 1.00) and proteinuria (2 studies, 49 participants: MD -1.98 g/24 h, 95% CI -2.89 to -1.07), without changing serum creatinine at 18 months (2 studies, 49 participants: MD -30.32 µmol/L, 95%CI -80.59 to 19.95).

Six months versus one year treatment with IFN resulted in differences terms of the maintenance of the response, 89% of patients in the six months group presented a relapse and only 11% maintained a long-term response at one year, while in the one year group only 78% relapsed and long-term response was observed in 22%. The one-year therapy was linked to a higher number of side-effects (severe enough to cause the discontinuation of treatment in two cases) than the six-month schedule.

One study reported immunoadsorption apheresis had uncertain effects on skin vasculitis (RR 0.44, 95% CI 0.05 to 4.02), peripheral neuropathies (RR 2.70, 95% CI 0.13 to 58.24), and peripheral joint arthralgia (RR 2.70, 95% CI 0.13 to 58.24), cryocrit (MD 0.01%, 95% CI -1.86 to 1.88) at six months, and no infusion reactions were reported. However when clinical scores were evaluated, they reported changes were more favourable in immunoadsorption apheresis with higher remission of severe clinical complications (80% versus 33%, P = 0.05) compared to immunosuppressive treatment alone.

In terms of death, it was not possible to present a pooled intervention effect estimate because most of the studies reported no deaths, or did not report death as an outcome.

Authors' conclusions

To treat HCV-associated mixed cryoglobulinaemia, it may be beneficial to eliminate HCV infection by using antiviral treatment and to stop the immune response by using rituximab. For skin vasculitis and for some laboratory findings, it may be appropriate to combine antiviral treatment with deletion of B-cell clonal expansions by using of rituximab. The applicability of evidence reviewed here is limited by the absence of any studies with direct-acting antivirals, which are urgently needed to guide therapy.

PLAIN LANGUAGE SUMMARY

Treatment for hepatitis C virus-associated cryoglobulinaemic vasculitis

What is the issue?

Nowadays, the second most frequent chronic viral infection in the world is hepatitis C virus (HCV) infection, before new direct-acting antiviral agents therapy has appeared. HCV causes chronic liver disease as well as extra-hepatic symptoms, one of the most common being mixed cryoglobulinaemia. Immunoglobulins that precipitate at low temperature (below 4°C) and re-dissolve after warming to 37°C are called cryoglobulins ("cryo" comes from the Greek word for cold). Cryoglobulinaemic vasculitis, which is the manifestation of an inflammation of small and medium-sized vessels produced by a pathogenic protein called IgM with rheumatoid factor activity generated by an expansion of B-cells. The immune complexes formed precipitate mainly in the skin, joints, kidneys and peripheral nerve fibres. We wanted to assess the effects of any treatment for skin, joints, kidneys or peripheral nerve fibres damage that occurs in HCV infection.

What did we do?

We identified 10 randomised controlled trials (RCT) enrolling 394 participants that met our inclusion criteria. This review looked at three possible strategies to control the disease and to investigate their impact on short and long-term outcomes: elimination of HCV infection by using interferon or new direct-acting antiviral agents, removal of cryoglobulins by using of immunoadsorption apheresis, or deletion of B-cell clonal expansions by using of rituximab. These strategies could be utilized in adults usually in combination with antiviral agents.

What did we find?

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Considering the limitation of the lack of studies with new direct-acting antiviral agents, some benefits in terms of skin, nerve or kidney illness where found when rituximab, antiviral treatment with IFN or immunoadsorption apheresis were used compared to using other immunosuppressive drugs. These three interventions were not compared head-to-head.

Conclusions

To treat HCV-associated mixed cryoglobulinaemia, it is always recommendable to eliminate HCV infection by using any antiviral treatment (in this review we only evaluated interferon treatment because no RCT with new antivirals looking at this disease have been published). Depending on the extend of mixed cryoglobulinaemia HCV-related disease it would be recommended to combine antiviral treatment with deletion of B-cell clonal expansions by using of rituximab or with removal of cryoglobulins by using of immunoadsorption because of their faster and more long-lasting improvement of skin, joints, kidneys or peripheral nerve fibres injury. Studies with new antivirals are urgently needed to guide therapy.