# Le manifestazioni extraepatiche da virus epatitici:

## Focus sugli effetti del trattamento con DAA e della pandemia da Covid-19 sulla CM correlata ai virus epatitici


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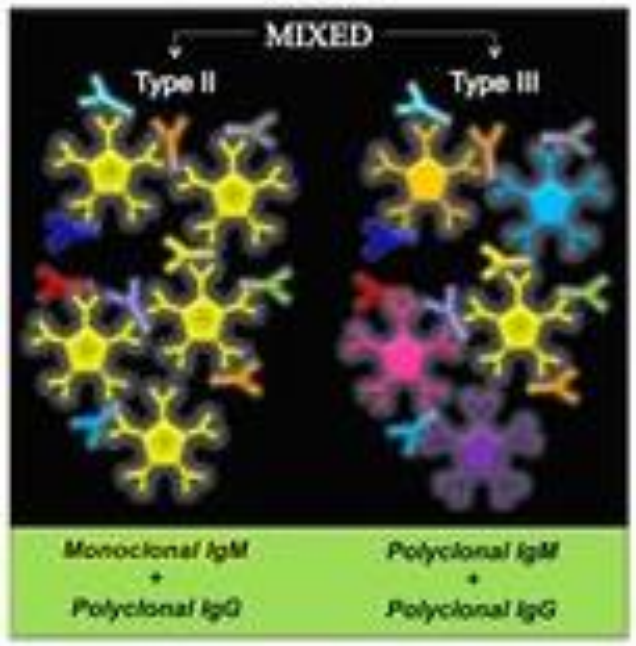
# Mixed Cryoglobulinemia Etiology




5-10% → Non-HCV-related (HBV, other)

90-95% → HCV-related

**Most (70–90%) MC+ are HCV+ and most HCV+ are CGs+ (40–60%); 5–30% of CGs+ have symptomatic MC (MCS or CV)**

(expected modification in prevalences, see Boleto et al, 2020)

# HCV-unrelated cryoglobulinaemic vasculitis: the results of a prospective observational study by the Italian Group for the Study of Cryoglobulinaemias (GISC)

M. Galli[1], L. Oreni[2], F. Saccardo[3], L. Castelnovo[4], D. Filippini[5], P. Marson[6], M.T. Mascia[7], C. Mazzaro[8], L. Origgi[9], E. Ossi[10], M. Pietrogrande[11], P. Pioltelli[12], L. Quartuccio[13], S. Scarpato[14], S. Sollima[15], A. Riva[16], P. Fraticelli[17], R. Zani[18], D. Giuggioli[19], M. Sebastiani[20], P. Sarzi Puttini[21], A. Gabrielli[22], A.L. Zignego[23], P. Scaini[24], C. Ferri[25], S. De Vita[26], G. Monti[27]

175 prospectively enrolled MC patients were followed up for 677 person-year

Associated conditions:

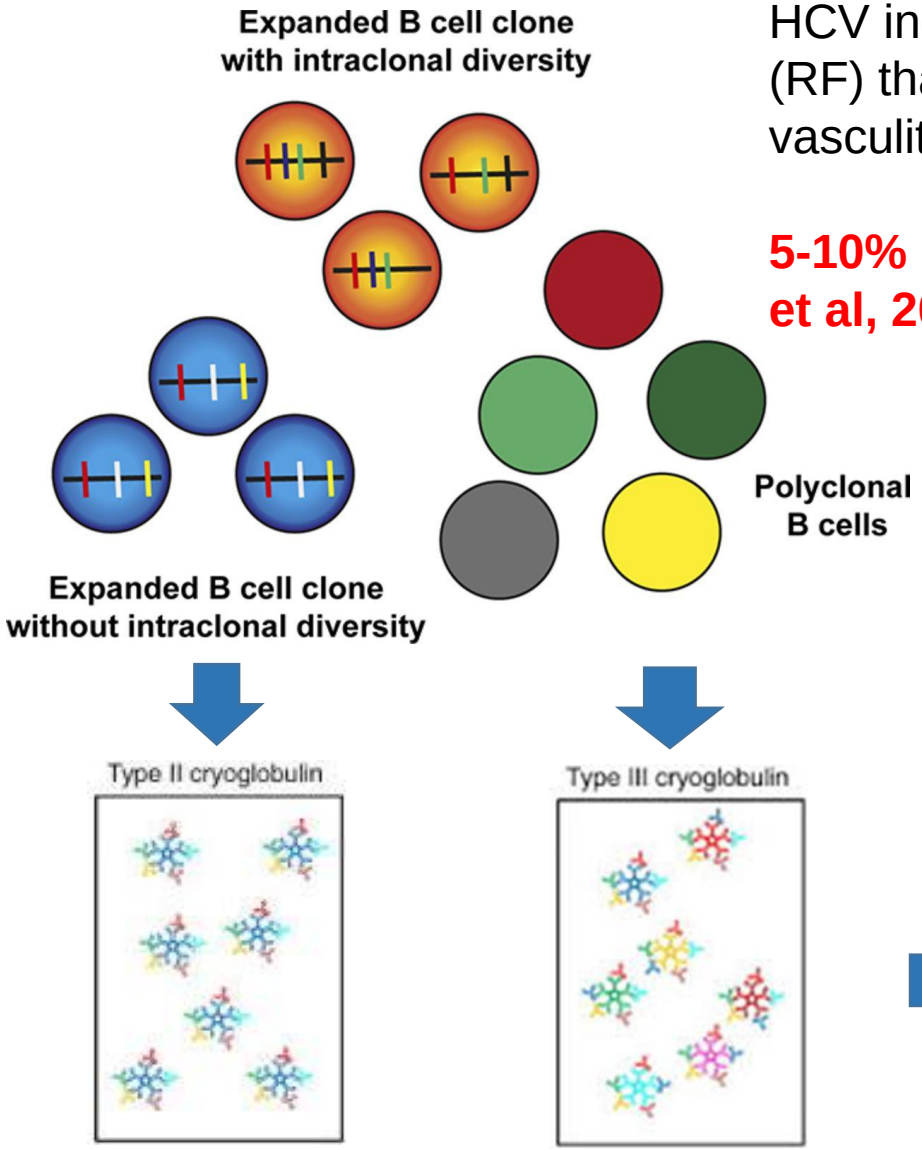
- primary Sjögren's syndrome (21.1%)
- SLE (10.9%) and other autoimmune disorders (10.9%)
- lymphoproliferative diseases (6.8%)
- solid tumours (2.3%)
- HBsAg positivity (8.6%)

39.4% patients had essential CV

HCV-unrelated CV is a multifaceted and often disabling disorder. The associated conditions influence its clinical severity, giving rise to significantly different clinical and laboratory profiles and outcomes.

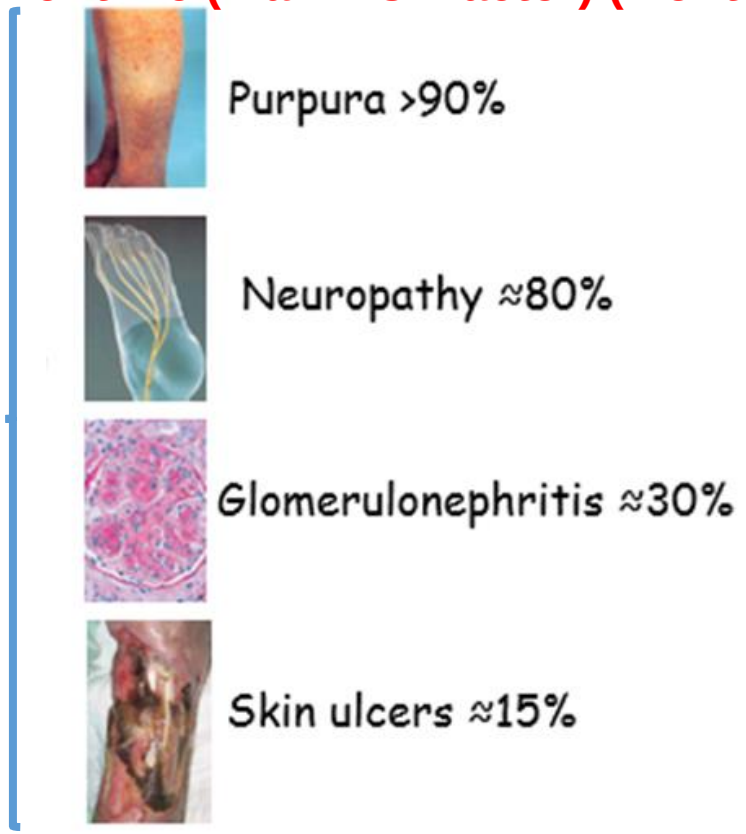
Clin Experimental Rheumatol 2017

# MIXED CRYOGLOBULINEMIA




HCV induces monoclonal expansion of B cells producing rheumatoid factor (RF) that forms cryoprecipitable immune complexes causing small vessel vasculitis

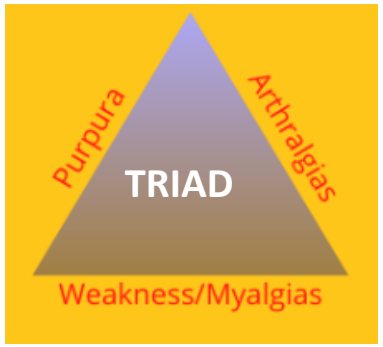
**5-10% of patients develop B-cell NHL over time (main risk factor) (Monti et al, 2005)**

# Main Clinical Manifestations of MCS/CV

**Male/Female: 1/3**
**Median age: 55 yrs**

**Fatigue** (98%)
**Purpura** (80-98%)
**Arthralgia** (91%)




- **Peripheral neuropathy** (81%)
- **Sicca syndrome** (51%)
- **Raynaud phenomenon** (32%)
- **Renal involvement** (30%)
- **Ulcers** (22%)
- **B-NHL** (5-10%)
- **CV involvement** (<1%)
- **CNS vasculitis** (<1%)
- **Interstitial lung disease**
- **Digestive involvement**
- **Fever-pruritus**

## Laboratory:

**Cryoglobulins**
**RF**
**Hypocomplementemia (C4)**

**Autoreactivity:**

ANA, AMA, Anti-GOR, ENA

*Ferri, Ramos-Casals, Zignego et al, 2016*

# General hypotheses proposed to elucidate HCV-induced LPD pathogenesis

1) Continuous external stimulation of lymphocyte receptors by viral antigens throughout persistent infection;

2) HCV replication in B cells with oncogenic effect mediated by intracellular viral proteins;

3) Mutation of tumor suppressor genes caused by a transiently present intracellular virus

Zignego et al, 2017

# General hypotheses proposed to elucidate HCV-induced LPD pathogenesis

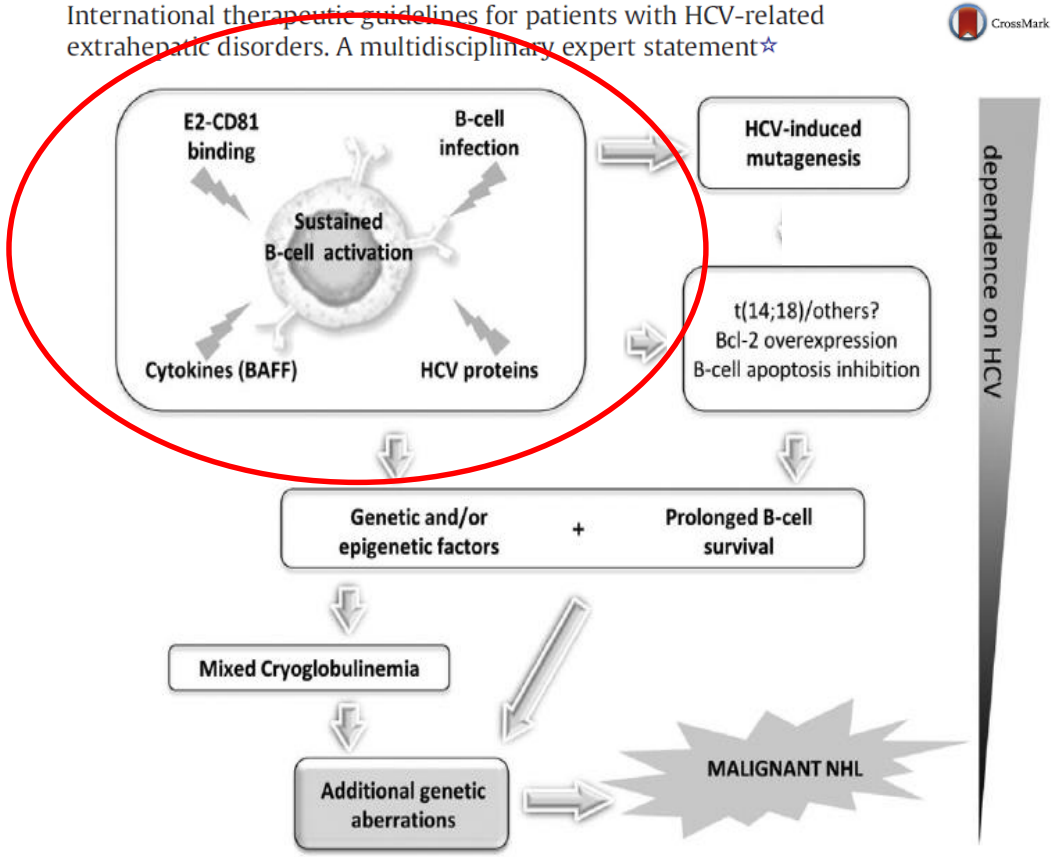
Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

International therapeutic guidelines for patients with HCV-related extrahepatic disorders. A multidisciplinary expert statement☆




Zignego et al, 2017

# Terapia della Crioglobulinemia Mista

## Terapie patogenetico/sintomatiche
**per il**
**disordine autoimmune/linfoproliferativo**

**Immunosoppressori (CYC, RTX*, CS)**

**Dieta ipoantigenica**

**Plasmaferesi**

**Antiflogistici (CS, colchicina)**

**Analgesici**

**Altri farmaci sintomatici**

Variamente combinate
Non modificano sostanzialmente la storia naturale della CM

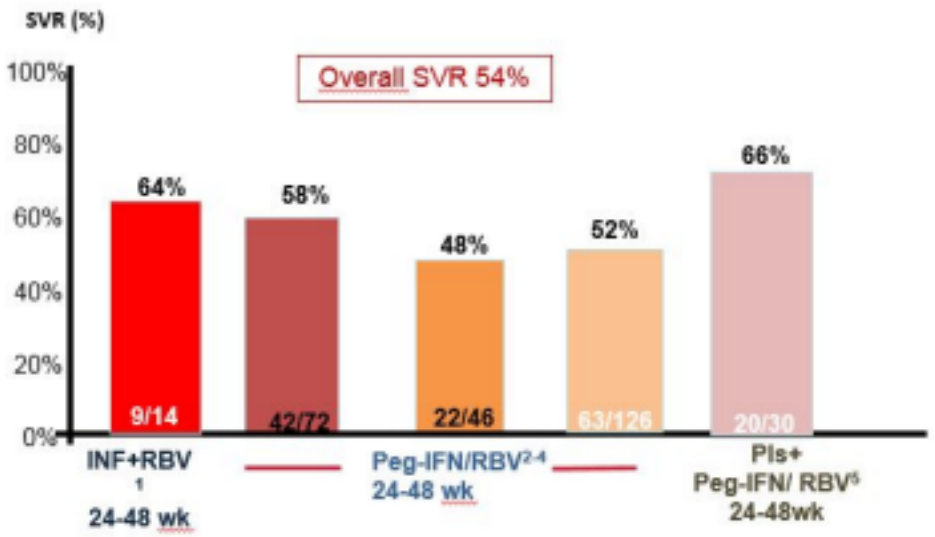
## Terapia Etiologica
**per le**
**CM correlate a virus epatitici**

**Terapia Antivirale**

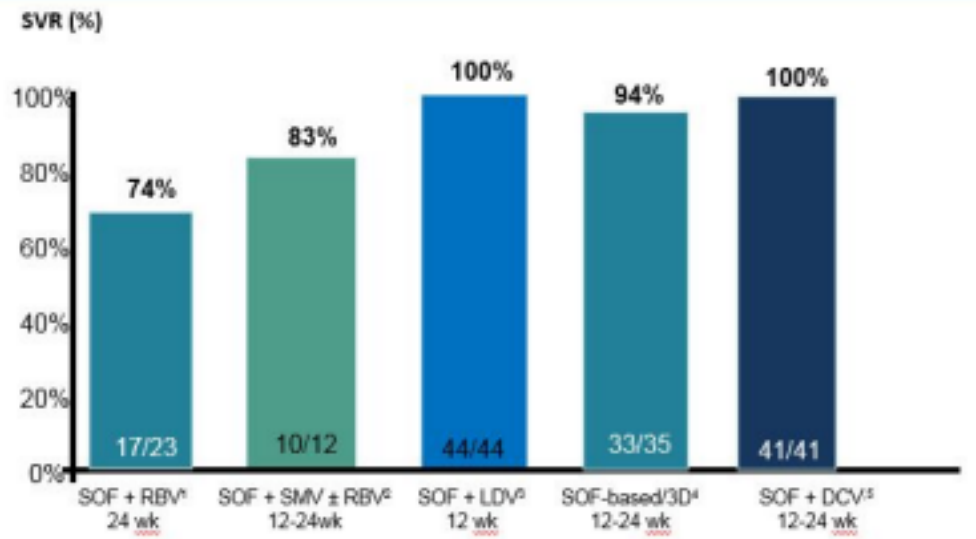
In grado di modificare sostanzialmente
la storia naturale della CM

# HCV-CV
# Virological Response after IFN-based vs IFN-free THerapy

## Virological Response after INF-based regimens




## Virological Response after INF-Free regimens





1. Cacoub Arth Rheum 2002;2. Saadoun Arth Rheum 2006;3. El Khayat Hepatol int 2012; 4. Gragnani Hepatology 2015; 5. Saadoun J Hepatol 2015
2. 1.Saadoun, Ann Rheum 2015; 2. Sise, Hepatology 2016 ;3. Gragnani, Hepatology 2016; 4. Bonacci, Clin Gastro Hepatol 2016 ; 5. Saadoun, Gastroenterology 2017


MASVE

# HCV-CV: Clinical Response following IFN-free Therapy

## CV Clinical Response: Classification Criteria

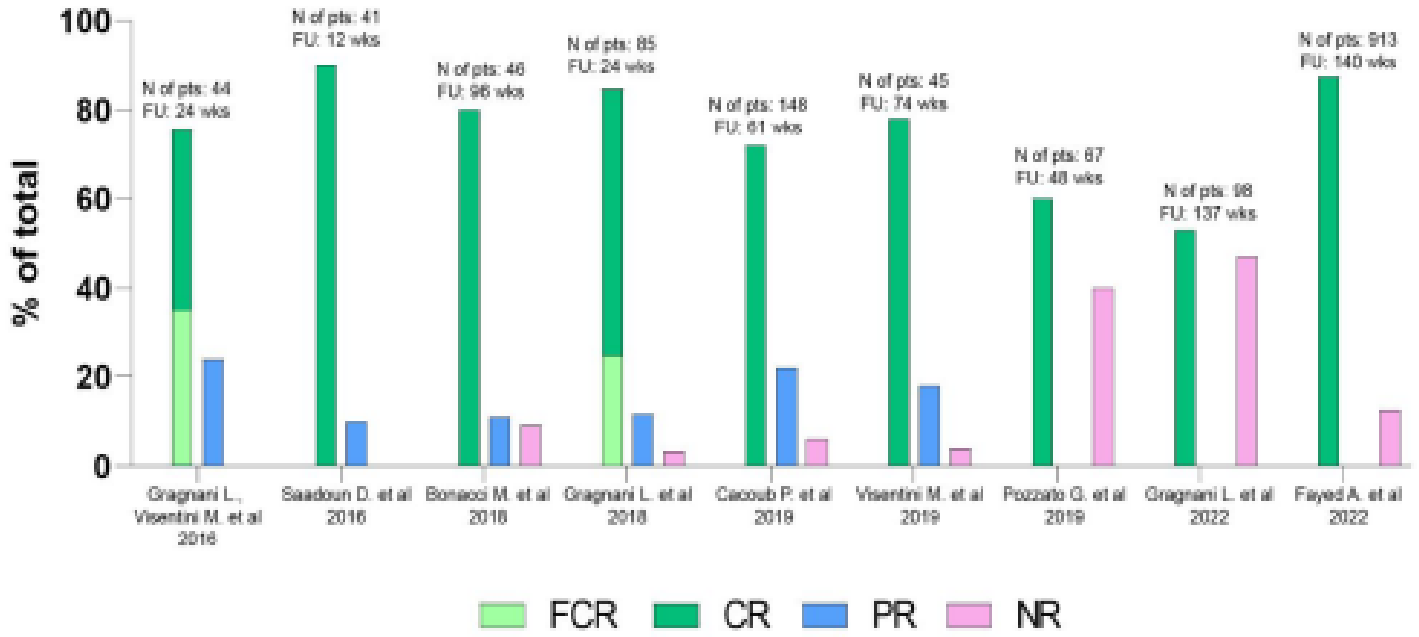
**Available data show that IFN-free AVT is safe, generally well tolerated and effective in MC patients: high rate of clinical response (87%) and low rates of serious adverse events was reported**

**Partial response (PR)**
Improvement of more than 50% of symptoms

**Complete response (CR)**
Improvement of all Symptoms

**Full complete response (FCR)**
Disappearance of all Symptoms
(*restitutio ad integrum*)

**Non-response (NR)**
Remaining conditions



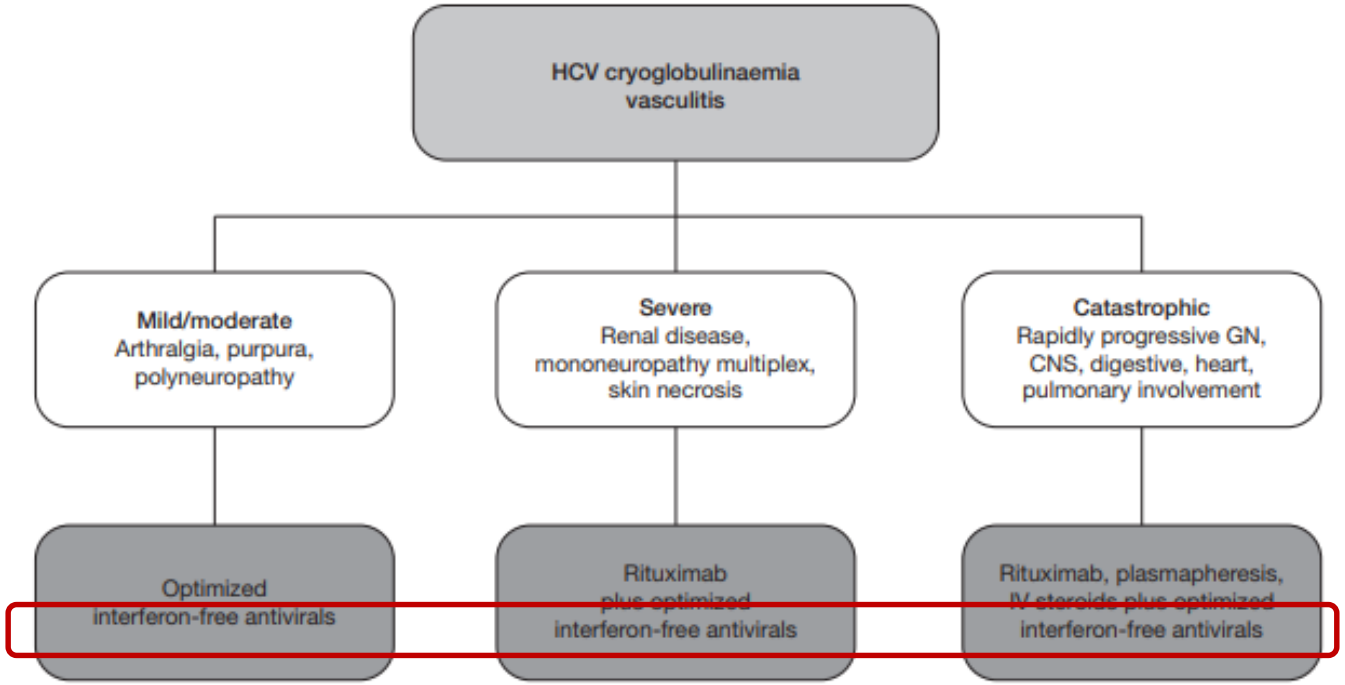

Zignego et al, Autoimmun. Rev. 2017, Saadoun D, *et al.* Ann Rheum Dis 2016; Sise M E *et al.* Hepatology 2016; Gragnani L, *et al.* Curr Drug Targets 2016; Gragnani L, *et al.* Hepatology 2016; Bonacci M, *et al*. Clin Gastroenterol Hepatol 2016; Weimer *et al.* Digest Liver Dis 2016.

# Expert opinion on managing chronic HCV in patients with mixed cryoglobulinaemia vasculitis

*Anna Linda Zignego[1], Jean-Michel Pawlotsky[2,3], Mark Bondin[4], Patrice Cacoub[5,6,7,8]**

Antiviral Therapy 2018;

Proposed treatment algorithm for HCV-associated mixed cryoglobulinaemia vasculitis |




Management of HCV CV should be individualized according to the severity of CV:

- Patients with mild-moderate CV should be treated only with DAAs
- In severe cases , RTX should also be administered, with plasmapheresis if necessary
- CS may be used to help control of minor inflammatory symptoms, whereas other immunosuppressant should only be given in cases of refractary CV

HEPATOLOGY AASLD 2021

# A prospective study of DAA Effectiveness and Relapse Risk in HCV Cryoglobulinemic Vasculitis by the Italian PITER Cohort

Loreta A Kondili, Monica Monti, Maria Giovanna Quaranta, Laura Gragnani, Valentina Panetta, Giuseppina Brancaccio, Cesare Mazzaro, Marcello Persico, Mario Masarone, Ivan Gentile, Pietro Andreone, Salvatore Madonia, Elisa Biliotti, Roberto Filomia, Massimo Puoti, Anna Ludovica Fracanzani, Diletta Laccabue, Donatella Ieluzzi, Carmine Coppola, Maria Grazia Rumi, Antonio Benedetti, Gabriella Verucchi, Barbara Coco, Liliana Chemello, Andrea Iannone, Alessia Ciancio, Francesco Paolo Russo, Francesco Barbaro, Filomena Morisco, Luchino Chessa, Marco Massari, Pierluigi Blanc, Anna Linda Zignego

*The presence of MC was not tested in >70% of cases in spite of its clinical, prognostic and therapeutical importance, and the diagnostic approach was variable (only in case of clinical suspicion in some centres)*
*Kondili L, Vella S, Zignego AL; PITER Collaborating group. Liver International 2017*

**.Total PITER HCV+ patients: 11.871**

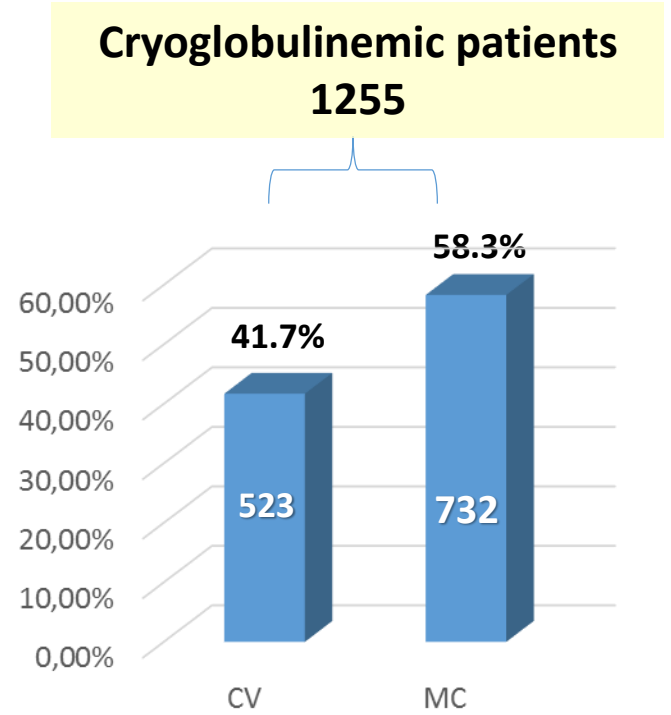
**.HCV+ patients evaluated: 3390 (28,5%)**

**.Cryoglobulinemic patients: 1255 (37%)**

**. with symptoms: CV 523/1255 (41,7%)**

**. asymptomatic: MC 732/1255 (58,3%)**

- **Type III in 33%**
- **Type II in 67%**



HEPATOLOGY AASLD

# A prospective study of DAA Effectiveness and Relapse Risk in HCV Cryoglobulinemic Vasculitis by the Italian PITER Cohort

## SVR CV Patients: Clinical CV Response EOT

PITER
Piattaforma Italiana per lo studio della Terapia delle Epatiti viRali.

1255 HCV cryoglobulinemic patients treated with DAAs

732 Patients without symptoms (MC)

523 patients with Cryoglobulinemic Vasculitis (cv)

100 lost during Follow-up

423 patients with available clinical data in different points of Follow-up after Sustained Virological Response (SVR)

EOT Response

PR: 28%

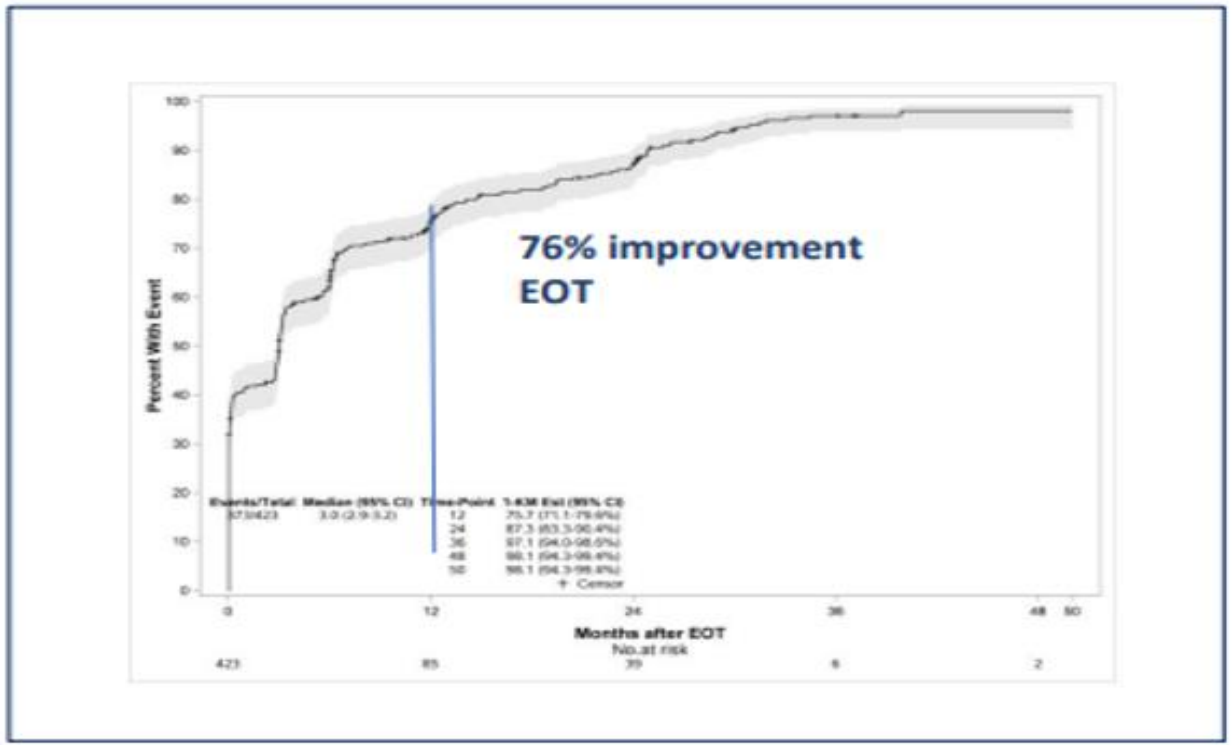
CR: 17%

FCR: 12%

Clinical Response: 57%

NR: 43%

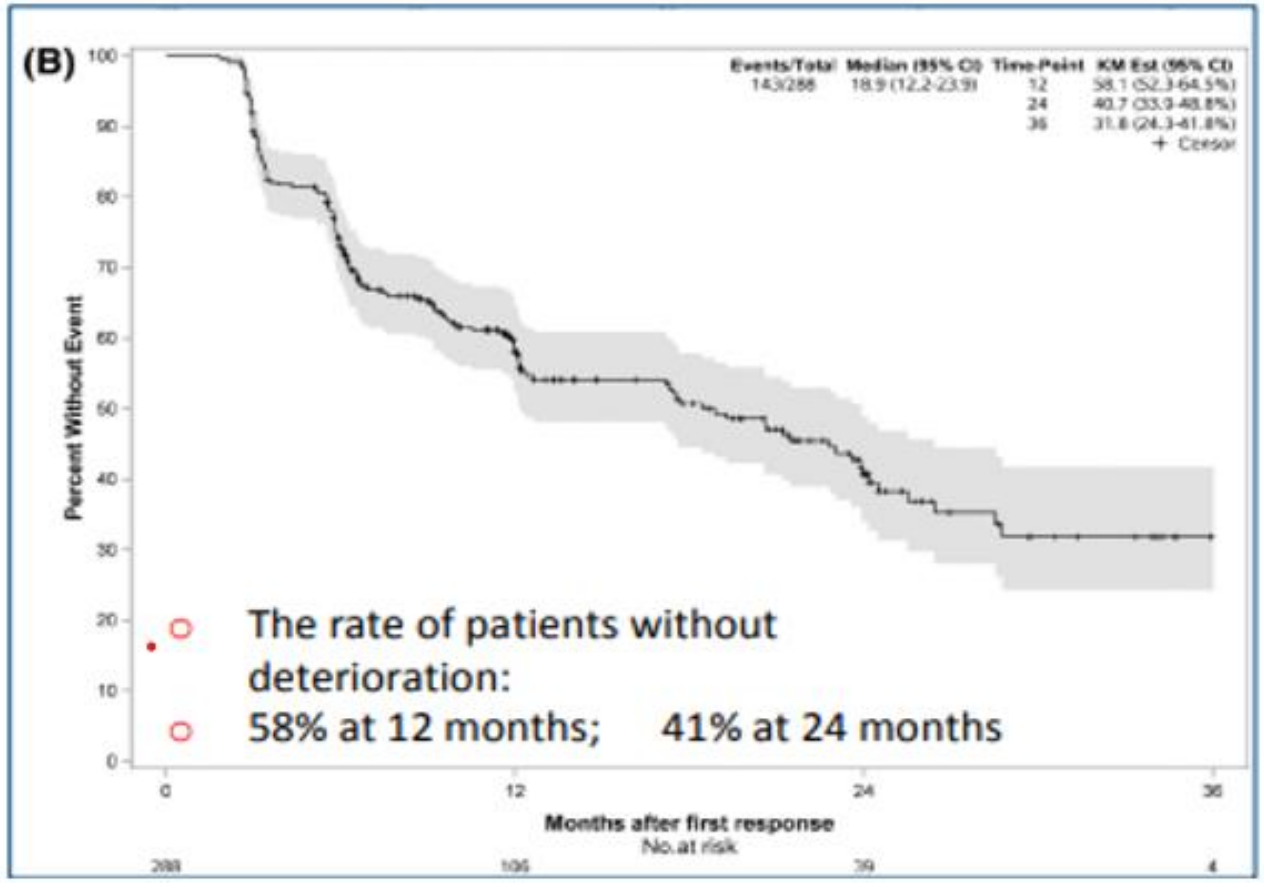
**Curve describing the first time in which a clinical response was observed after EOT**




- Firts amelioration starting after EOT (about 3 m)
- Further improvement in 50% during 1-2yrs F-U
- Clinical response during FU in 88%
- FCR in about 30% during F-U

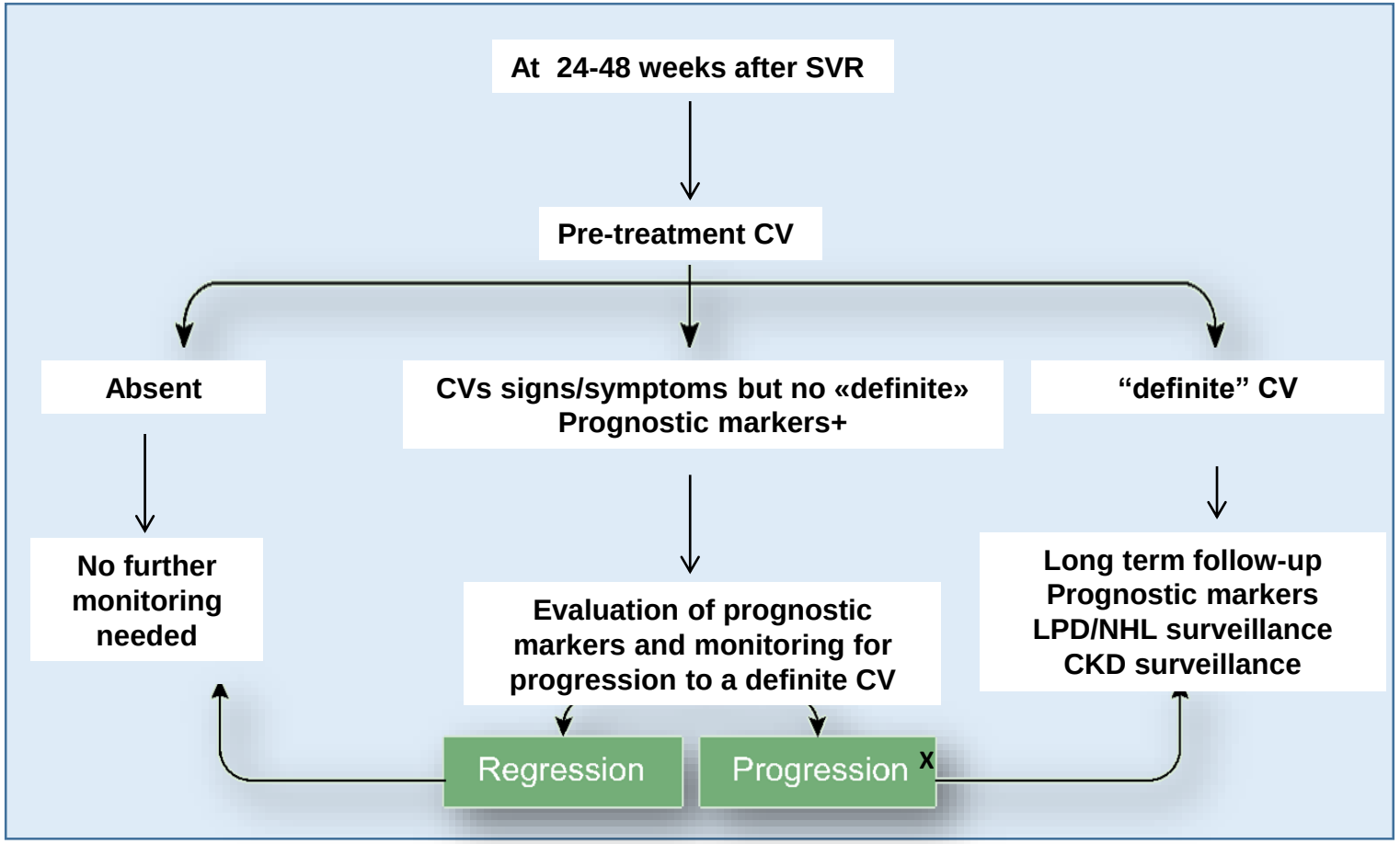
# The MC Clinical Response after DAAs: a Fluctuating Picture

**Curve of CV clinical deterioration or relapse occurring during the FU after the first clinical response following HCV eradication**




- **Clinical deterioration or relapse in about 49% CV (med. time 19 m.)**
- **Relapse after FCR in 13% (transient in 70%)**

# Taylored Post AVT Follow-Up of HCV-MC Patients




*Consider RTX treatment in persisting B-cell clonality

Prognostic Factors:

- Laboratory: Clonality Biomarkers* (FLC k/Lambda ratio, T(14;18)); Genetic Biomarkers (Notch4 polymorphism)*; high cryocrit**; high RF values*/**
- Demographical/Clinical: Age; Neuropathy; Weakness; SS; CKD**
- CV and Global Severity Indexes***

*Gragnani et al, Hepatology 2020; **Kondili et al, Hepatology 2022; ***Ferri et al, Autoimmune Rev, 2022

viruses

MDPI

*Review*

# Hepatitis B Virus-Related Cryoglobulinemic Vasculitis: Review of the Literature and Long-Term Follow-Up Analysis of 18 Patients Treated with Nucleos(t)ide Analogues from the Italian Study Group of Cryoglobulinemia (GISC)

Suppression of HBV chronic infection by **NAs** is the first-line treatment for HBV-related CV (effectiveness of PEG-IFN-α is inconsistent)

**Rituximab** is effective for NR or relapsing patients or for patients with severe or life-threatening CV (glomerulonephritis, peripheral neuropathy, extended cutaneous ulcers, gastrointestinal vasculitis, acute hyper-viscosity syndrome); **NAs must always be associated**, due to the risk of viral reactivation in HBV+ subjects, including those with OBI

**Plasmapheresis** may be indicated in severe and life-threatening HBV-CV. However, it should be used very cautiously in patients with cirrhosis

Low-dose and long-term treatments with **CS** should not be used for the significant side effects. However, such a treatment may be helpful if administered as short-term courses for chronic pain control

**MILD**

Purpura, fatigue, arthralgia, low-grade fever

- Tenofovir/entecavir

**MODERATE TO SEVERE**

Skin ulcers, glomerulonephritis, peripheral neuropathy

- Tenofovir/entecavir with:
- Plasma exchange with or without high-dose corticosteroids
- Rituximab in refractory disease

**LIFE-THREATENING**

Rapidly progressive glomerulonephritis, haemorragic alveolitis, abdominal vasculitis, CNS vasculitis, hyperviscosity syndrome

- Tenofovir/entacavir with:
- Plasma exchange with high-dose corticosteroids
- Rituximab in refractory disease

# Flares of CV after Vaccination Against SARS-CoV-2

*Visentini M, Gragnani L, Santini SA, Urraro T, Villa A, Monti M, Palladino A, Petraccia L, La Gualana F, Lorini S, Marri S, Madia F, Stefanini S, Basili S, Fiorilli M, Ferri C, Zignego AL, Casato M, 2022*

- Flares in 6/63 (9.5%) CV patients: did not endanger patients and subsided spontaneously thus reassuring the safety of SARS-CoV-2 vaccination in patients with MC
- Anti-SARS-CoV-2 IgG responses: seronegative 11.6% RTX-free and 71% RTX treated patients (p=0.002)
- Seronegativity was more frequent (p=0.04) among patients with EMC than in SVR HCV-MC, suggesting lower immune dysregulation due to reversion of B cell abnormalities after clearance of infection

These observations encourage administering vaccine booster to patients with MC and postponing vaccination of RTX-treated patients after B cell repopulation

| Patient | Age (years)/ sex | MC type | SVR (months) | Last active symptoms and RTX before vaccination (months) | | Vaccine | Symptoms after first dose | Symptoms after second dose |
|---|---|---|---|---|---|---|---|---|
| | | | | Symptoms | RTX | | | |
| 1 | 70/male | EMC | N/A | P (40) | N/T | AstraZeneca | Diffuse P (day 3) | Second dose refused |
| 2 | 41/female | EMC | N/A | P (20) | 20 | Pfizer | None | Diffuse P (day 1) |
| 3 | 76/female | EMC | N/A | P (27) | N/T | Pfizer | None | Diffuse P (day 5) |
| 4 | 57/female | HCV-MC | 67 | PN (42) | N/T | Pfizer | None | Moderate P, PN (day 10) |
| 5 | 66/female | HCV-MC | 62 | P, PN (48) | N/T | Pfizer | None | Moderate P, PN (day 7) |
| 6 | 63/female | HCV-MC | 30 | P, PN (26) | N/T | Pfizer | None | Moderate P (day 7) |

BMJ Journals
Annals of the Rheumatic Diseases

# COVID-19 and MCS. Long-term survey study on the prevalence and outcome, vaccine safety and immunogenicity. Gragnani L et al, 2023, in press

- 430 unselected CV patients
- From February 2020 to October 2021
- Enrolled by 11 referral centers
- 502 healthy controls

| | Total CV population N=430 | CV subsets | | | | p |
|---|---|---|---|---|---|---|
| | | HCV-related (a) N=334* | HBV-related (b) N=10 | Essential (c) N=47 | Overlap syndromes (d) N=39° | |
| **Age mean ± SD yrs (range)** | 70 ± 10.96 (26-94) | **71.2± 10.96 (26-94)** | 66.3 ± 10.9 (40-78) | 69 ± 11 (40-86) | **67.3 ± 10.3 (48-82)** | **a vs d 0.03** |
| **F/M ratio** | 300/130 (2.3) | **232/102 (2.3)** | **4/6 (0.66)** | **30/17 (1.8)** | **34/5 (6.8)** | **a vs d 0.02 b vs d 0.004 c vs d 0.01** |
| **Disease duration, mean ± SD years** | 8.9 ± 05 | **9.5 ± 6.2 (2-38)** | 6.9 ± 4.7 (2-16) | **6.6 ± 5 (1-22)** | 8.4 ± 6.3 (1-27) | **a vs c 0.0002** |

The clinical status of CV patients and the possible development of COVID-19 were evaluated by survey using a standardized symptom-assessment questionnaire every 6 months, or in the event of significant clinical variations

**NAb dosage timing**

# COVID-19 prevalence, death and relapse rate in CV

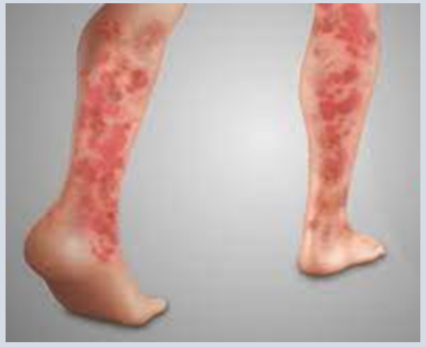
## PREVALENCE

- SARS-CoV-2 infection was recorded in **51/430 patients (11.9%)**= **significantly higher compared to the Italian general population** (National update of Task force, ISS, October 2021) over the same timeframe (11.9% vs 8.0%, p<0.005);

## DEATH RATE

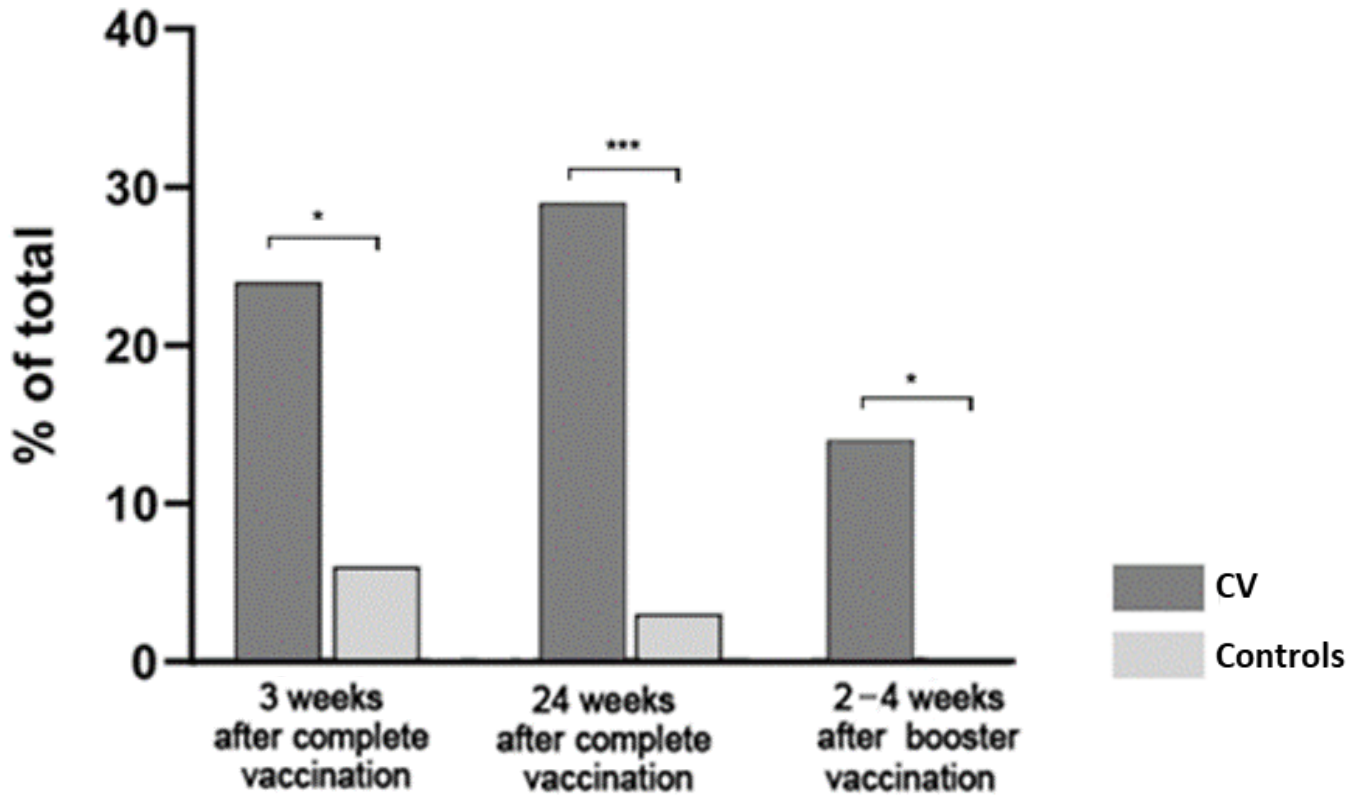
- COVID-19-related **death rate was increased in CV** (5.9%) compared to Italian general population (2.76%); the death rate (3/51, 5.9%) in CV patients with COVID-19 was significantly higher than that recorded in the COVID-19-negative group (deaths due to malignant neoplasia: 2/379, 0.5%; p<0.01)

## CV FLARES



- CV flares following COVID-19 vaccination were observed in 5% of cases (20/374);
- **INTERESTINGLY** the prevalence of CV flares possibly triggered by vaccination was significantly lower than that caused by SARS-CoV-2 infection (20/374, 5% vs 10/51, 14%; p=0.0285).

# No response rate at the three time-points in CV compared to controls




As expected, CV patients on immune-modifier treatments (mostly RTX and glucocorticoids) showed a higher prevalence of a no response or a sub-optimal response (10/16, 63%) compared to those without immune-modifiers (8/29 (28%), p=0.0298).

A.L.CRI.
Associazione Italiana per la Lotta contro le Crioglobulinemie

Clinical and Experimental
RHEUMATOLOGY

**COVID-19 vaccination rate and safety profile in a multicentre Italian population affected by mixed cryoglobulinaemic vasculitis 2022**

Vacchi C , Testoni S, Visentini M, Zani R, Lauletta G, Gragnani L, Filippini D, Mazzaro C, Fraticelli P, Quartuccio L, Padoan R, Castelnovo L, Zignego AL, Ferri C, Scarpato S, Casato M, Hoxha M, Salvarani C, Monti G, Galli M, Sebastiani M

MCV pts were assessed with an interview-based survey about vaccination, reasons for not getting vaccinated, adverse events (AE), and disease flares within a month after vaccination

416 pts; 7.7% did not get vaccinated, mainly for fear related to vaccine side-effects (50%) or medical decision (18.8%)
post-vaccination vasculitis flares were observed in 5.3% of subjects, mainly in pts with neuropathy or skin vasculitis (40% and 25%, respectively)

Vasculitis flares rate was in line with that observed for other autoimmune diseases

Hesitancy, rituximab and glucocorticoids treatment were the main reasons for delaying vaccination.

# COVID-19/COVID-19 VACCINES AND PATIENTS WITH ASD

**Covid-19 and Autoimmune Systemic Diseases (ASD) patients.** Ferri C et al, 2021

3,029 unselected ASD patients/ 36 tertiary referral centers (multicenter telephone 6-week survey)

Higher prevalence of Covid-19 vs general population (p=.000)

*Need to develop targeted prevention/management strategies during the current pandemic wave*

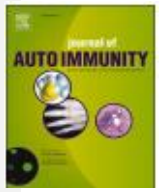

**Impaired immunogenicity to COVID-19 vaccines in ASD. High prevalence of non-response in different subgroups** Ferri C et al, 2021

Prospective observational multicenter study

478 ASD patients (including 61 CV). Serum NAb (SARS-CoV-2 IgG II Quant antibody test , Abbott) on samples obtained within 3 weeks after vaccination

Lower NAb levels and higher percentage of non-responders in ASD patients vs controls [$p < 0.0001$] especially in patients treated with CS, mycophenolate-mofetil , or RTX

*Patients with suboptimal response should be prioritized for a booster-dose of vaccine, while a different type of vaccine could be administered to non-responder individuals*

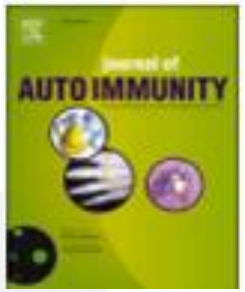



**Prevalence and death rate of Covid-19 in ASD in the first 3 pandemic waves. Relationship with disease subgroups and ongoing therapies.** Ferri C et al, 2021

3,918 ASD pts consecutively recruited by a telephone survey

Higher prevalence of COVID-19 in ASD ($p<0.0001$) with major adverse prognostic factors to develop COVID-19 including older age, male gender, SSc, pre-existing interstitial lung involvement, and long-term CS treatment

# COVID-19/COVID-19 VACCINES AND PATIENTS WITH ASD




**Absent or suboptimal response to booster dose of COVID-19 vaccine in patients with ASDs.** *Ferri C et al, 2022*

Serum IgG-neutralizing antibody (NAb) in: 478 ASD patients originally evaluated after the first vaccination cycle (time 1), 344 individuals re-evaluated after 6-months (time 2), 244 after the booster vaccine dose (time 3)
In pts receiving booster vaccine (3), the mean serum NAb levels were constantly lower vs controls ($p < 0.0001$), but increased compared to the first two
Treatment with immune-modifiers increased the percentage of patients with absent/suboptimal response ($p = 0.0031$)
*In this particularly frail patients' setting, tailored vaccination and/or therapeutic strategy are highly advisable*


**COVID-19 vaccine immunogenicity in 16 patients with ASD. Lack of both humoral and cellular response to booster dose and ongoing disease modifying therapies.** *Gragnani L et al. 2022*

Serum NAb titer and T-cell response (measuring IFN–γ- release) 3 weeks after the COVID-19 vaccine booster dose in 17 pts with ASDs vs 17 HCs
Lower NAb levels in ASD compared to HCs ($p < 0.0001$) with higher percentage of negative/sub-optimal humoral response
Lower levels of IFN-γ for both Ag1 and Ag2 as well lower rate of adequate T-cell response in ASD vs HCs, (0.0066).
Disease modifying therapies (DMT) were administered in all patients with deficient NAb production
*The impaired immunogenicity to COVID-19 vaccine booster and even more the concomitant lack of both humoral and cellular response might represent a high risk for severe COVID-19, particularly in ASD patients undergoing DMT.*

## I vaccini non causano malattie autoimmuni Maurizio de Martino, 2017

L'ipotesi:

Stimolare il sistema immunitario con gli antigeni dei vaccini, od anche con gli adiuvanti e le altre componenti delle preparazioni dei vaccini, può indurre lo sviluppo di una reazione autoimmune:

- si basa esclusivamente su casi aneddotici o studi osservazionali non controllati in cui viene descritto lo sviluppo di meccanismi autoimmuni che sono però fugaci e che comunque non determinano l'innesco di malattie autoimmuni per i robusti meccanismi di controllo del sistema immunitario
- In talune condizioni è stato dimostrato un nesso causale fra vaccinazione e sviluppo di autoimmunità (es. piastrinopenia autoimmune e vaccino anti-morbillo, rosolia e parotite). Ma questa si sviluppa molto più frequentemente a seguito delle tre infezioni, per cui il bilancio è largamente favorevole alla vaccinazione.

## L'adiuvante nei vaccini: è davvero un problema? Simeone G e Cinicola BL. RIAP 2018

Le reazioni avverse locali e/o sistemiche osservate in seguito alla somministrazione di un vaccino adiuvato potrebbero essere legate al meccanismo d'azione degli adiuvanti di iperattivazione immunologica spesso mediata dal rilascio di citochine pro-infiammatorie

Tuttavia, gli studi epidemiologici finora non sono riusciti a fornire una connessione certa

### Scheda segnaletica sui vaccini a mRNA anti-COVID-19

| Vaccino / Proprietà | Comirnaty® (3 diverse formulazioni autorizzate) | Spikevax® |
|---|---|---|
| Denominazione tecnica | BNT162b2 | mRNA-1273 |
| Titolare dell'omologazione | Pfizer/BioNTech, USA/D | Moderna, USA |
| Tipo di vaccino | Vaccino a mRNA | |
| Composizione degli antigeni | Proteina spike SARS-CoV-2 | |
| Adiuvante | Nessuno. L'mRNA è contenuto in particelle lipidiche. | |
| Additivi potenzialmente allergenici | ~~In particolare glicole polietilenico (PEG o macrogol), trometamina/trometanolo (TRIS; in Spikevax®~~ e nelle seguenti formulazioni di Comirnaty®: 10 µg/dose (tappo arancione) per bambini dai 5 ai 12 anni e 30 µg/dose dispersione per preparazione iniettabile (tappo grigio)) | |
| Indicazione prevista dall'omologazione | Immunizzazione attiva per la protezione dalla COVID-19 causata dal virus SARS-CoV-2 | |
| | A partire dai 5 anni (3 formulazioni con indicazioni specifiche) | A partire dai 6 anni[1] |
| Dosaggio dell'immunizzazione di base | 2 dosi i.m.[2] | |
| | Intervallo minimo: 21 giorni[3], intervallo raccomandato: 28 giorni | A distanza di almeno 28 giorni[3]<br>Bambini tra i 6 e gli 11 anni: dose ridotta (50 µg) |
| Efficacia | Protezione da una malattia COVID-19 sintomatica dopo 2 dosi di vaccino | |
| | Persone a partire dai 16 anni[4]: 95% (95% CI 90–98%)<br>Adolescenti dai 12 ai 15 anni[4]: 100% (95% CI 75–100%)<br>Bambini dai 5 agli 11 anni[5]: 90,7% (95% CI 67,7–98,3%) | Persone a partire dai 18 anni[4]: 94% (95% CI 89–97%)<br>Adolescenti dai 12 ai 17 anni[4]: 100% (95% CI 29–NE%)<br>Bambini tra i 6 e gli 11 anni[6]: 88 % (95 % CI 70,0–95,8 %) |

# SARS-CoV-2 vaccines and autoimmune diseases amidst the COVID-19 crisis

Tsvetelina V., Tsvetoslav G., 2021

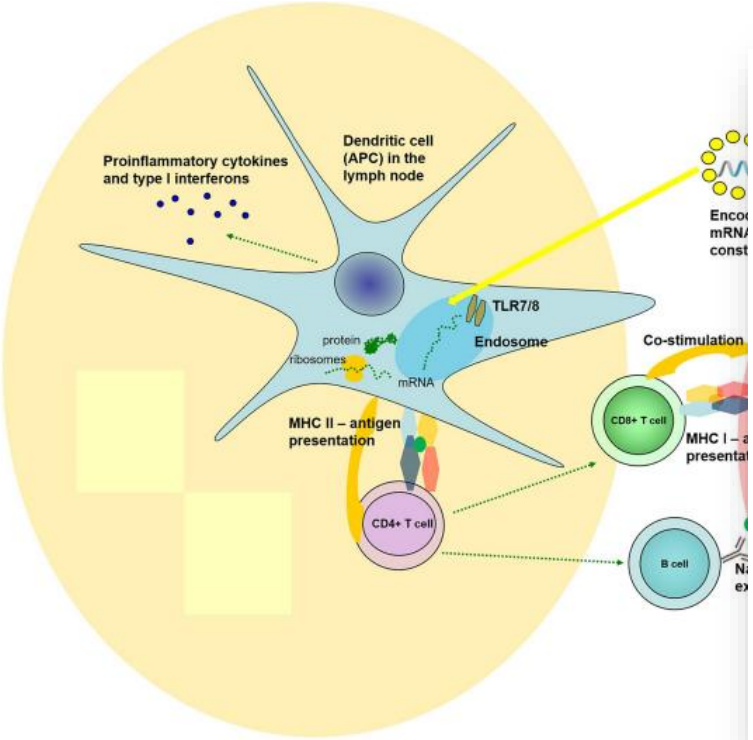
Rheumatology
INTERNATIONAL

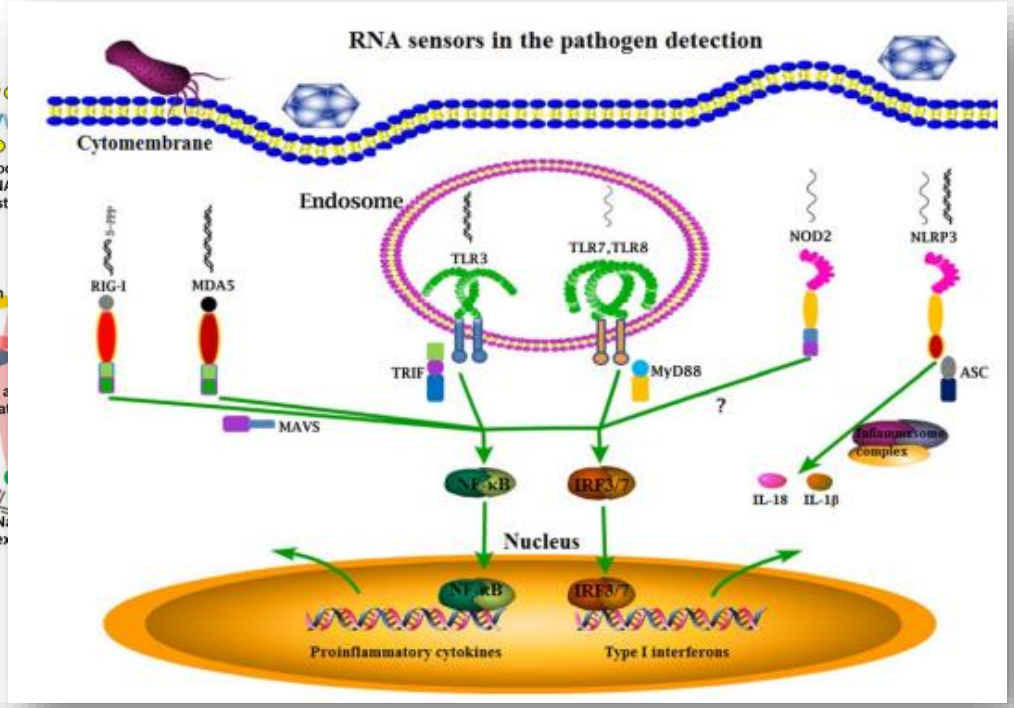
At the current phase of the COVID-19 pandemic, it is essential to discriminate between those who will benefit most from the vaccination and those who may have reasonable concerns regarding vaccination

For the AIID patients, the theoretical risk for relapse of the autoimmune disease is related to mRNA's properties

## IMMUNE PROCESSES INVOLVED IN THE MECHANISM OF mRNA VACCINES

- Activation of CD4+ via MHC I molecules and processed viral Ag in APCs in lymph-node
- Stimulation of CD8+ via MHC II and processed viral Ag and B cells
- In APCs mRNA sense TLR7 and 8 with production of proinflammatory cytokines and IFN type I




Overall the effects of mRNA vaccines are desirable, considering the viral mechanisms of inhibiting IFNs and other arms of the immune system, but they may contribute to the non-specifc activation of autoreactive lymphocytes leading to higher risk of relapse of an AIID (or hypothetically developing de novo AIID)

Real-world data on COVID19 vaccines in patients with AIIDs are limited = need for further studies!

# CONCLUSIONS

- Establishing proper recommendations for the newly developed vaccines against SARS-CoV-2 would be challenging: vaccine administration has been associated with clinical flares in systemic autoimmune diseases/MC patients = need for a taylored approach

- The associated vaccination risk should not lead to vaccine refusal or major delay in these patients who will soon have at their disposal different vaccine platforms with variable safety and cost-effectiveness profiles

- insufficient data: patients with systemic autoimmune disorders/MC need to be included in the ongoing clinical trials to ensure vaccine safety and efficacy in the context of an autoimmune disease= appropriate trials would clarify the underlying immunological mechanisms of the newly implemented vaccines/adjuvants in the AIIDs population