

Prof. Clodoveo Ferri

Curriculum Vitae

<i>Nato:</i>	Cropani (CZ) il 22 marzo 1947
<i>Albo professionale:</i>	Ordine dei Medici Provincia di Pisa
<i>Qualifica:</i>	Professore Ordinario di Reumatologia
<i>Titoli di Studio:</i>	1972: Laurea con Lode in Medicine e Chir., Università di Pisa 1978: Specializzazione in Reumatologia, Università di Pisa 1979: Specializzazione in Medicina Interna, Università di Pisa

Attività assistenziale & accademica:

- **1972-2002:** UOC e Cattedra Reumatologia, Università di Pisa
- **Fino al 31 nov 2017: direttore UOC di Reumatologia, Azienda Ospedaliero-Universitaria Policlinico di Modena**
Direttore Cattedra e Scuola di Specializzazione di Reumatologia, Univ. di Modena e Reggio E. (scuola capofila Emilia R. e Marche
Direttore Centro Interdipartimentale malattie rare del polmone (MaRP)
- **Dal settembre 2012: Presidente del Collegio Professori Ordinari di Reumatologia**
- **Componente Commissione Nazionale per ASN-MIUR nel SC 06/D3 dal dicembre 2016.**

Appartenenza a Società Scientifiche:

Società Italiana di reumatologia (SIR)
Gruppo Italiano per lo Studio delle Crioglobulinemie (GISC)
International Fellow American College of Rheumatology (ACR)

Attività di Ricerca

- **Ruolo eziopatogenetico di differenti virus nelle malattie autoimmuni e linfoproliferative:**
 - a. identificazione dell'HCV come principale fattore trigger della vasculite crioglobulinemica (crioglobulinemia mista);
possibile ruolo di HEV e HBV nella crioglobulinemia mista
 - b. identificazione dell'HCV come fattore trigger in una significativa percentuale di linfomi non-Hodgkin a cellule B
 - c. ruolo dell'HCV nella porfiria cutanea tarda
 - d. ruolo dell'HCV nel carcinoma papillare della tiroide
 - e. ruolo del HCMV e del PV-B19 nella sclerosi sistemica (sclerodermia)
- **Studi sierologici e trials clinici in differenti malattie reumatiche:** artrite reumatoide, LES, sclerosi sistemica, vasculiti sistemiche
- **Studi di eziopatogenesi, clinico-terapeutici e di survival su:**
vasculite crioglobulinemica
- **Studi di eziopatogenesi, clinico-terapeutici e di survival su:**
fenomeno di Raynaud e sclerosi sistemica
- **Ruolo terapeutico della plasmaferesi e di una dieta ipoantigenica in malattie autoimmuni:** vasculite crioglobulinemica, LES, sclerodermia, IgA nephropathy.

Principali risultati dell'attività di ricerca:

- **23 capitoli** su textbooks nazionali ed internazionali
- **oltre 350 articoli** su riviste internazionali
- **seminari e letture** su invito presso molte università italiane e straniere (compreso NIH di Bethesda USA) ed a numerosi congressi nazionali ed internazionali
- numerosi **riconoscimenti** a livello internazionale dei risultati raggiunti con l'attività di ricerca, in particolare della scoperta del legame eziopatogenetico fra infezione da HCV e vasculite crioglobulinemica (1991) e linfomi non-Hodgkin (1994): vedi *Haematologica Editorial* 1996
- **progetto PRIN 2015-2018** (Bando 2015 Prot. 2015YZB22C) su virus linfotropi e malattie autoimmuni sistemiche, in qualità di centro proponente/coordinatore (gruppi partecipanti Univ. di Modena, Ferrara, Parma e Firenze).
- riconosciuta idoneità a svolgere il ruolo di **commissario** per Concorso Abilitazione Scientifica Nazionale (ASN), MIUR settore concorsuale 06/D3.
- **H-index:** da Scopus 61; da Google 67; Top Italian Scientists 67

TIS List in: Modena e Reggio Emilia

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Rank	Academic	H-index	Nation	Area	MacroArea	Italian Institution	note
1	Leonardo M Fabbri	105	Italy	clinical - medicine	Clinical Sciences	Modena e Reggio Emilia	Verified Google Scholar MyCitations Last Update: 10/10/2017
2	Bruno Calabretta	71	USA	immunology - medicine	Biomedical Sciences	e Modena e Reggio Emilia	
3	Andrea Cossarizza	71	Italy	cell biology	Biomedical Sciences	Modena e Reggio Emilia	Verified Google Scholar MyCitations Last Update: 07/08/2017
4	Clodoveo Ferri	67	Italy	clinical - medicine	Clinical Sciences	Modena e Reggio Emilia	Verified Google Scholar MyCitations Last Update: 17/08/2017
5	Enrico Bonatti	64	Italy/USA	earth sciences	Natural & Environmental Sciences	CNR Bologna e Modena e Reggio Emilia	Verified Google Scholar MyCitations Last Update: 06/08/2017
6	Stefano Cascinu	61	Italy	cancer - medicine	Biomedical Sciences	Modena e Reggio Emilia	Verified Google Scholar MyCitations Last Update: 25/10/2017
7	Antonello Pietrangelo	60	Italy	clinical - medicine	Clinical Sciences	Modena e Reggio Emilia	Verified Google Scholar MyCitations Last Update: 07/10/2017
8	Giuseppe Boriani	59	Italy	cardiology - medicine	Biomedical Sciences	Modena e Reggio Emilia	Verified Google Scholar MyCitations Last Update: 22/10/2017
9	Franco Zambonelli	56	Italy	computer sciences	Computer Sciences	Modena e Reggio Emilia	Verified Google Scholar MyCitations Last Update: 31/10/2017
10	Fabio Biscarini	55	Italy	chemistry - nanotechnology	Material & Nano Sciences	Modena e Reggio Emilia	Verified Google Scholar MyCitations Last Update: 16/10/2017
11	Elisa Molinari	52	Italy	physics	Physics	Modena e Reggio Emilia	Verified Google Scholar MyCitations Last Update: 17/10/2017
12	Andrea Cornia	52	Italy	chemistry	Chemistry	Modena e Reggio Emilia	Verified Google Scholar MyCitations Last Update: 21/08/2017
13	PC Marchisio	52	Italy	mol cell biology	Biomedical Sciences	Modena e Reggio Emilia e S. Raffaele Milano	
14	Massimo Federico	52	Italy	cancer - medicine	Biomedical Sciences	Modena e Reggio Emilia	Verified Google Scholar MyCitations Last Update: 30/09/2017
15	F Mavilio	51	Italy	genetics - medicine	Biomedical Sciences	Modena e Reggio Emilia e S. Raffaele Milano	
16	Cristina Mussini	50	Italy	medicine	Clinical Sciences	Modena e Reggio Emilia	Verified Google Scholar MyCitations
17	Giovanni Pellacani	48	Italy	dermatology - medicine	Clinical Sciences	Modena e Reggio Emilia	Verified Google Scholar MyCitations

Pubblicazioni:

1. capitoli di libri

1. Moriconi L, Di Munno O, Pugliese F, Ferri C, Tartarelli G, Gremignai G, Ciabattini G, Cioni L, Bombardieri S.: Plasma exchange and renal prostaglandins in lupus nephritis. *Progress in Artificial Organs*, edited by Y. Nosé, C. Kjellestrand and P. Ivanovich, ISAO Press, Cleveland 1986, p.846 -850.
2. Pasero G, Ferri C: La terapia aferetica in reumatologia. *Progressi in Medicina Interna: Reumatologia*. A cura di G. Danieli, UTET-Torino 1990; pag. 583-606.
3. Migliorini P, Tincani A, Ferri C, Balestrieri G, Bombardieri S: Solubilizzazione degli Immunocomplessi (ICSC) e inibizione della precipitazione immune (ICPIC) nella Crioglobulinemia Mista Essenziale. In: *Immunologia : Attualità e prospettive*. Il Pensiero Scientifico Editore, pag. 508-512, 1983.
4. Bombardieri S, Tavoni A, Mosca M, La Civita L, Dolcher MP, Lombardini F, Migliorini P, Ferri C: Mixed cryoglobulinemia: the role of HCV and organ-specific antibodies. In B Ansell, PA Bacon, JT Lie, H Yazici (Eds.): *The Vasculitides*. Chapman & Hall, London, 1996, pp. 283-93.
5. Della Rossa A, Ferri C, Bombardieri S: From essential mixed cryoglobulinemia to virus-induced autoimmunity: ten years of research on mixed cryoglobulinemia. In Y Shoenfeld, ed. *The decade of autoimmunity*. Elsevier Science B.V. 1999; p. 235-243.
6. **Ferri C, Pileri S, Zignego AL: Hepatitis C Virus, B-cell Disorders, and Non-Hodgkin's Lymphoma. In; Infectious Causes of Cancer. Targets for Intervention. Goedert JJ, ed. NIH, National Cancer Institute. The Humana Press Inc. Totowa, New Jersey; 2000: p. 349-368.**
7. Ferri C, Bombardieri S: HCV and cryoglobulinemia. In: *Infections and autoimmunity*. Y Shoenfeld & N Rose, editors. Elsevier BV; 2004: p. 203-214.
8. **Ferri C, Zignego AL, Pileri S: Cryoglobulins. Chapter 24. Textbook 'Clinical Hematology'. Elsevier (Mosby): 2005.**
9. Ferri C, Mascia MT: Mixed cryoglobulinemia. In *'The Skin in Systemic Autoimmune Diseases'*. Elsevier: 2005.
10. **Ferri C, Mascia MT, Saadoun D, Cacoub P. Cryoglobulinemia and systemic manifestations of hepatitis C virus. EULAR compendium on rheumatic diseases, 2009. Chapter 42a.; pp 616-635. London, BMJ Publishing Group Ltd, 2009. http://www.eular.org/edu_compendium.cfm**
11. SA Pileri, C Agostinelli, C Campidelli, F Bacci, E Sabattini, M Giunti, A Pileri, M Piccioli, S Righi, M Rossi, C Ferri and PP Piccaluga: Chronic inflammation, including autoimmunity, and lymphomagenesis. Chapter 26. *Magrath: The Lymphoid Neoplasms*, 3rd Edition, 2010. GPS Publishing Solutions, UK.
12. Ferri C, Colaci M, Manfredi A. Vasculiti sistemiche (capitolo 165) in: G. Gasbarrini, A. Gasbarrini, A. Rossi, *Trattato di Medicina Interna*, Verduci 2011.
13. Antonelli A, Ferri C, Fallahi Poupack. The endocrinology of liver disease. Chapter 10.2.2. Wass JAH and Stewart PM: *Oxford Textbook of Endocrinology and Diabetes*. 2nd Edition. Oxford.
14. Antonelli A, Ferri C, Ferrari SM, Colaci M, Corrado A, Di Domenicantonio A, Fallahi P. Endocrine Manifestations of HCV-Positive Cryoglobulinemia (chapter 24) in: F. Dammacco (ed.), *HCV Infection and Cryoglobulinemia*, Springer-Verlag Italia 2012
15. Antonelli A, Ferri C, Ferrari SM, Colaci M, Ruffilli I, Mancasi C, Ferrannini E, Fallahi P. Serum a-Chemokine CXCL10 and b-Chemokine CCL2 Levels in HCV-Positive Cryoglobulinemia (chapter 17) in: F. Dammacco (ed.), *HCV Infection and Cryoglobulinemia*, Springer-Verlag Italia 2012

16. Ferri C, Antonelli A, Sebastiani M, Colaci M, Zignego AL. The Expanding Spectrum of Clinical Features in HCV-Related Mixed Cryoglobulinemia. (chapter 19) in: F. Dammacco (ed.), *HCV Infection and Cryoglobulinemia*, Springer-Verlag Italia 2012
17. **Ferri C, Sebastiani M, Saadoun D, Cacoub P. Cryoglobulinemia and hepatitis C virus. EULAR compendium on rheumatic diseases, 2012. Chapter 42; pp 1042-1071. Ed. JWJ Bijlma. London, BMJ Publishing Group Ltd, 2012.**
18. C. Ferri, M. Colaci, D. Giuggioli: Vasculiti ANCA associate. In: Malattie Autoimmuni Sistemiche. Ed. Roberto Perricone. Capitolo 25; p. 491-512. Società Editrice Universo 2013.
19. Clodoveo Ferri, Dilia Giuggioli, and Marco Sebastiani: Cryoglobulinemic Vasculitis. In Vasculitis: Symptoms, Diagnosis and Treatment; Update. Chapter 10. Ed.: D. Younger. © Nova Science Publishers, Inc. 2013
20. Clodoveo Ferri, Marco Sebastiani, Dilia Giuggioli. Vasculiti dei piccoli vasi. In: Reumatologia. Ed. UNIREUMA; Idelson-Gnocchi 2013.
21. Clodoveo Ferri, Marco Sebastiani, Dilia Giuggioli, Poupack Fallahi, and Alessandro Antonelli: Cryoglobulins and Cryoglobulins Secondary to Hepatitis C Virus Infection. In: Autoantibodies. Third Edition. Ed.: E Gershwin, Y Shoenfeld, PL Meroni. Elsevier 2014.
22. Bernini L, Manzini CU, Ferri C. BCG and autoimmunity. In Vaccines and Autoimmunity. Chapter 21, Page 197. Edited by Yehuda Shoenfeld, Nancy Agmon-Levin, Lucija Tomljenovic. Wiley-Blackwell 2015.
23. **Ferri C, Sebastiani M, Saadoun D, Cacoub P. Cryoglobulinemia and hepatitis C virus. EULAR compendium on rheumatic diseases, 2012. Chapter 42; pp 1042-1071. Ed. JWJ Bijlma. London, BMJ Publishing Group Ltd, 2015.**
New Edition 2018 in press

2. articoli su riviste internazionali

1. Bellina CR, Bianchi R, Bombardieri S, Ferri C, Mariani G, Muratorio A, Rossi B. Quantitative evaluation of ^{99m}Tc-pyrophosphate muscle uptake in patients with inflammatory and noninflammatory muscle diseases. *J Nucl Med Allied Sci.* 1978 Apr-Jun;22(2):89-96.
2. Bombardieri S., Paoletti P., Ferri C., Di Munno O., Fornai E., Giuntini C.: Lung involvement in essential mixed cryoglobulinemia. *Am J Med* 66, 748-756, 1979.
3. Bombardieri S, Ferri C, Di Munno O, Pasero G. Liver involvement in essential mixed cryoglobulinemia. *Ric Clin Lab.* 1979 Oct-Dec;9(4):361-8.
4. Moriconi L., Ferri C., Paleologo M., Migliorini P., Fanara G., Gremignai G., Cioni L., Bombardieri S.: Plasma exchange in systemic lupus erythematosus. *Artificial Organs* 5 (Suppl.): 172-174, 1981.
5. Pasero G, Di Munno O, Ferri C, Riente L. [Minor connectivitis and the mixed connective tissue disease] *Minerva Med.* 1980 Apr 14;71(15):1117-22.
6. Bombardieri S., Ferri C., Paleologo G., Bibolotti E., Camici M., Fosella P.V., Pasero G., Moriconi L. : Prolonged Plasma-exchange in the treatment of renal involvement in essential mixed cryoglobulinemia. *Int J Art Organs* 6, S-1, 47-50,
7. Moriconi L., Ferri C., Fanara G., Migliorini P., Vitali C., Cioni L., Gremignai G., Bombardieri S. : Plasma exchange in the treatment of Lupus nephritis. *Int J Art Organs* 6(S-1): 35-38, 1983.
8. Balestrieri G, Tincani A, Migliorini P, Ferri C, Cattaneo R, Bombardieri S - Inhibitory effect of IgM rheumathoid factor on the immune complex solubilization capacity and on the inhibition of immune precipitation. *Arthritis Rheum.* 27, 1130-1136, 1984.
9. Ghione S., Meconi P., Fommei E., Palombo C., Pecori F., Moriconi L., Ferri C.: The blood pressure lowering effects of plasma exchange. *Int J Art Organs* 8(S-2): 13-14, 1984.
10. Paleologo G., Moriconi L., Puccini R., Pasquariello A., Innocenti M., Lippi A., Gadducci P., Marianetti G., Ferri C., Cioni L.: Plasma exchange in unusual forms of rapidly progressive glomerulonephritis. *Int J Art Organs* 8(S-2): 60, 1984
11. Bombardieri S, Ferri C, Migliorini P, Puccetti A, Vitali C, Moriconi L, Fosella PV: Immune complex behaviour during prolonged plasma exchange in essential mixed cryoglobulinemia and systemic lupus erythematosus. *Int J Art organs* 8(S-2): 7-10, 1985.
12. Ferri C., Bernini L., Bongiorno M.G., Levorato D., Bravi P., Viegi G., Contini C., Pasero G., Bombardieri S.: Noninvasive evaluation of cardiac dysrhythmias and their relationship with multisystemic symptoms, in progressive systemic sclerosis patients. *Arthritis Rheum* 28: 1259-1266, 1985.
13. Puccini R, Fommei E, Meconi P, Moriconi L, Palombo C, Pasquariello A, Ferri C, Cioni L, Ghione S: Hypotensive effect of plasma exchange in immune complex nephritis. *Artificial Organs* 9(1): 42-46, 1985.
14. Moriconi L, Palombo C, Fommei E, Meconi P, Puccini R, Innocenti M, Ferri C, Pecori F, Ghione S: Acute effect of plasma exchange on arterial blood pressure and plasma renin activity. *Artificial Organs* 9(3): 276-273, 1985.
15. Ruffatti A, Calligaro A, Ferri C, Bombardieri S, Gambari PF, Todesco S. Association of anti-centromere and anti-Scl 70 antibodies in scleroderma. Report of two cases. *J Clin Lab Immunol.* 1985 Apr;16(4):227-9.
16. Ghione S, Meconi P, Fommei E, Palombo C, Mezzasalma L, Pecori F, Moriconi L, Ferri C. The blood pressure lowering effects of plasma exchange. *Int J Artif Organs.* 1985 Jul;8 Suppl 2:13-4.
17. Ferri C, Bernini L, Bombardieri S, Pasero G - Long-term treatment of progressive systemic sclerosis with griseofulvin. *Scand J Rheum* 15:356-362, 1986.

18. Ferri C, Moriconi L, Gremignai G, Migliorini P, Paleologo G, Fosella PV, Bombardieri S - Treatment of renal involvement in essential mixed cryoglobulinemia with prolonged Plasma Exchange. *Nephron* 43, 246-251, 1986.
19. Barbieri P., Benedettini G., Ferri C., Campa M., Bombardieri S.: Lymphocyte subpopulation in essential mixed cryoglobulinemia. *J Rheumatol* 13:108-112,1986.
20. Vitali C., Vieggi G. Tassoni S., Tavoni A., Paoletti P., Bibolotti E., Ferri C., Bombardieri S. : Lung function abnormalities in different connective tissue diseases. *Clin. Rheumatology* 5: 181-188, 1986.
21. Bombardieri S, Ferri C, Migliorini P, Pontrandolfo A, Puccetti A, Vitali C, Pasero G. Cryoglobulins and immune complexes in essential mixed cryoglobulinemia. *Ric Clin Lab.* 1986 Apr-Jun;16(2):281-8.
22. Ferri C, Gremignai G, Bombardieri S, Moriconi L, Pontrandolfo A, Vitali C, Fosella PV, Pasero G. Plasma-exchange in mixed cryoglobulinemia. Effects on renal, liver and neurologic involvement. *Ric Clin Lab.* 1986 Apr-Jun;16(2):403-11.
23. Moriconi L, Ferri C, Puccini R, Casto G, Baronti R, Cecchetti R, Gremignai G, Cioni L, Bombardieri S: Double filtration plasmapheresis in the treatment of cryoglobulinemic glomerulonephritis. *Int J Art Org* 12/S4: 83-86,1989.
24. Bombardieri S, Caponi L, Pilo A, Moriconi L, Ferri C, Puccetti A: Changes of the putative antigen/antibody ratio of circulating immune complexes following selected removal of macromolecules in mixed cryoglobulinemia and systemic lupus erythematosus. *Int J Art Org* 12/S4: 87-91,1989.
25. Pecori F, Ferri C, Moriconi L, Casto G, Grazzini R, Cecchetti R, Bombardieri S, Gremignai G, Barbani N, Chelli E, Foselle PV: T cell subset modifications induced by apheretic therapy of immunological diseases. *Int J Art Org* 12/S4: 97-100, 1989.
26. Vieggi G, Fornai E, Ferri C, Di Munno O, Begliomini E, Vitali C, Melocchi F, Bombardieri S, Paoletti P: Lung function in essential mixed cryoglobulinemia: a short-term follow-up. *Clin Rheumatol* 8:331-338, 1989.
27. Puccini R., Ferri C, Neri R, Palmieri L, Pecori F, Gremignai G, Gazzetti P, Cioni L, Bombardieri S, Moriconi L: The evaluation of certain biocompatibility parameters during apheretic therapy of immunological diseases. *Int J Art Org* 12/S4: 117-20, 1989.
28. Ferri C, Pietrogrande M, Cecchetti C, Tavoni A, Cefalo A, Buzzetti G, Vitali C, Bombardieri S: Low-antigen-content diet in the treatment of mixed cryoglobulinemia patients. *Am J Med* 87: 519-24, 1989.
29. Ferri C, Mannini L, Bartoli V, Gremignai G, Genovesi-Ebert F, Cristofani R, Albanese B, Pasero G, Bombardieri S: Blood viscosity and filtration abnormalities in mixed cryoglobulinemia patients. *Clin Exp Rheumatol* 8: 271-281, 1990.
30. Ferri C, Greco F, Longombardo G, Palla P, Marzo E, Moretti A. Hepatitis C virus antibodies in mixed cryoglobulinemia. *Clin Exp Rheumatol* 9: 95-96, 1991.
31. Galli M, Invernizzi F, Pietrogrande M, Renoldi P, Colasanti G, Musicco M, Monti G, Monteverde A, Bombardieri S, Ferri C, Quintiliani L, Gabrielli A, Mussini C, Migliaresi S, Ossi E, Vacca A, Schena P, Pioltelli P, Dell'Aglio PP, Merlini GP, Mazzaro C: Cryoglobulinaemia and serological markers of hepatitis viruses. *Lancet* 338ii: 758-9, 1991.
32. Ferri C, Marzo E, Longombardo G, Lombardini F, Greco F, Bombardieri S: Alpha-interferon in the treatment of mixed cryoglobulinemia patients. *Proceedings International Cancer Update. Focus on interferon alfa-2b', Cannes, Nov 1990. Eur J Cancer* 27 (S4): 81-82, 1991.
33. Ferri C, Greco F, Longombardo G, Palla P, Marzo E, Moretti A, Fosella PV, Pasero G, Bombardieri S: Hepatitis C virus antibodies in mixed cryoglobulinemia patients. *Arthr Rheum* 34: 1606-1610, 1991.
34. Ferri C, Greco F, Longombardo G, Palla P, Marzo E, Moretti A, Fosella PV, Pasero G, Bombardieri S: Antibodies against hepatitis C virus in mixed cryoglobulinemia patients. *Infection* 19: 417-420, 1991.

35. Ferri C, Greco F, Longombardo G, Palla P, Marzo E, Moretti A, Mazzoni A, Pasero G, Bombardieri S, Highfield P, Corbishley T: Association between hepatitis C virus and mixed cryoglobulinemia. *Clin Exp Rheumatol* 9: 621-624, 1991.
36. Ferri C, Bernini L, Cecchetti R, Neri R, Latorraca A, Marotta G, Pasero G, Bombardieri S: Cutaneous and serological subsets of systemic sclerosis. *J Rheumatol*, 18:1826-1832, 1991.
37. Ferri C, Puccini R, Paleologo G, Longombardo G, Migliorini P, Moriconi L: IgA nephropathy: preliminary results of low-antigen-content diet treatment. *Arch Intern Med* 152: 437-438, 1992.
38. Ferri C, Bernini L, Gremignai G, Latorraca A, Fazzi P, Tavoni A, Solfanelli S, Bombardieri S: Lung involvement in systemic sclerosis sine scleroderma treated by plasma exchange. *Int J Art Org* 15: 363-368; 1992.
39. Ferri C, La Civita L, Cirafisi C, Siciliano G, Longombardo G, Bombardieri S, Rossi B: Peripheral neuropathy in mixed cryoglobulinemia: clinical and electrophysiological investigations. *J Rheumatol* 19: 889-895, 1992.
40. Ferri C, Cecchetti R, Cini G, Gambini I, La Civita L, Latorraca A, Bernini L, Bombardieri S, Pasero G: Effect of slow-releasing nicardipine in the treatment of isolated Raynaud's phenomenon patients. *Clin Rheumatol* 11: 76-80, 1992.
41. Bombardieri S, Ferri C: Low antigen content diet in the management of immuno-mediated diseases. *Isr J Med Sci* 28: 117-120; 1992.
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44. Neri R, Tavoni A, Cristofani R, Levanti C, Sodini G, d'Ascanio A, Vitali C, Ferri C, Bombardieri S: Antinuclear antibody profiles in Italian patients with connective tissue diseases. *Lupus* 1: 221-227; 1992.
45. Ferri C, Marzo E, Longombardo G, Lombardini F, La Civita L, Vanacore R, Liberati AM, Gerli R, Greco F, Moretti A, Monti M, Gentilini P, Bombardieri S, Zignego AL: Alpha-Interferon in Mixed Cryoglobulinemia patients: a randomized crossover controlled trial. *Blood* 81: 1132-1136; 1993.
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50. Pasquariello A, Ferri C, Moriconi L, La Civita L, Longombardo G, Lombardini F, Greco F, Zignego AL: Cryoglobulinemic membranoproliferative glomerulonephritis associated with hepatitis C virus. *Am J Nephrol* 105: 300-304, 1993.
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54. Ferri C, Baicchi U, La Civita L, Greco F, Longombardo G, Mazzoni A, Careccia G, Bombardieri S, Pasero G, Zignego AL, Manns MP: Hepatitis C virus-related autoimmunity in patients with porphyria cutanea tarda. *Eur J Clin Invest* 23: 851-855, 1993.
55. Ferri C, La Civita L, Longombardo G, Lombardini F, Pasero G, Zignego AL, Monti M, Mazzaro C, Greco F, Mazzoni A: Hepatitis C virus in mixed cryoglobulinemia and B-cell lymphoma. *Clin Exp Rheumatol* 12: 89-90, 1994.
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57. Ferri C, Pitaro N, Giuggioli D, Martini A, Carabelli E, Giraldi G, Muratorio A: Nailfold capillary microscopy in lacunar infarction. *Stroke* 25: 525-526, 1994.
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HEPATIS C VIRUS: A LINKAGE BETWEEN HEMATOLOGY AND HEPATOLOGY ESTABLISHED THROUGH MAJOR CONTRIBUTIONS BY ITALIAN RESEARCH

In this issue of *Haematologica*, Luppi and Torelli analyze the pathogenetic role of some lymphotropic viruses in human lymphoproliferative disorders¹. This has been a field of active research in the last few years, and we should be proud of the fact that important investigations on the relationship between hepatitis C virus (HCV) and lymphoproliferative disorders have been performed in Italy. In addition, Torelli and coworkers have made important contributions to studies on herpesviruses.

The dose association between HCV infection and mixed cryoglobulinemia (MC) represented the first evidence that this virus may have an etiopathogenetic role in lymphoproliferative disorders. Ferri *et al.*² investigated the prevalence of HCV infection of peripheral blood mononuclear cells in a series of 16 patients with type II mixed cryoglobulinemia. Previous exposure to HCV was shown in all cases (100%); moreover, HCV RNA was detected in peripheral lymphocytes from 13 out of the 16 patients, whereas it was never found in mononuclear blood cells from 20 control subjects. These findings strongly suggested that HCV infection might be responsible for the clonal B-cell expansion underlying the systemic manifestations of MC.

Pozzato *et al.*³ studied the clinical, histologic, and virologic findings of 31 patients affected with mixed cryoglobulinemia. The prevalence of anti-HCV antibodies was high (84%); polymerase chain reaction amplification of the 5' untranslated region of HCV was positive in 84% of subjects, and core region amplification was positive in 96%. A high prevalence of genotype II was found (77%), and chronic liver disease was present in 48% of patients. Bone marrow biopsy specimens showed the presence of low-grade non-Hodgkin's lymphomas in 12 cases (39%), whereas infiltration appeared to be reactive rather than monoclonal in 11 patients. This study confirmed that mixed cryoglobulinemia is closely associated with HCV infection since only

one patient was apparently not infected by the virus, and suggested that this disease is associated with a high prevalence of low-grade non-Hodgkin's lymphomas (NHLs).

The same authors investigated the long-term effects of α -interferon on clinical, hematological and virological parameters in a group of 18 patients affected with type II mixed cryoglobulinemia⁴. A bone marrow biopsy was performed in all patients, and a liver biopsy was obtained in those with biochemical signs of chronic liver disease. All patients followed the same treatment schedule: three million units of recombinant interferon- α sc., three times a week for 1 year. In 5 cases bone marrow histology showed the presence of a monoclonal lymphocytic infiltrate. Liver biopsies were performed in 13 (72%) of the patients and chronic liver disease was found in all 13. Anti-HCV antibodies were present in 17 (95%) subjects. HCV-RNA was detected in all cases (100%) before therapy. Five (28%) patients achieved a complete response and 9 (50%) a partial response, while the others (4 cases, 22%) showed minor responses. Four patients cleared the virus and obtained a complete remission of the MC. This study confirmed that HCV may be a cause of mixed cryoglobulinemia and suggested that α -interferon may be an effective agent for the treatment of this disorder.

At this point Ferri *et al.* decided to investigate HCV infection in a series of 50 unselected Italian patients with B-cell NHL.⁵ Antibodies against HCV were found in 30% of NHL, and HCV viremia in 32% of cases. HCV-related markers were detected in 34% (17/50) of NHL patients; this prevalence is particularly significant when compared with HCV seropositivity in Hodgkin's disease (3%) and healthy controls (1.3%). These data have been confirmed by Cavanna *et al.*⁶

Franzin *et al.*⁷ investigated clonal expansions of IgM-producing B cells in 38 patients with a



Clodoveo Ferri LUMIÈRE SUR LE FROID

Sans doute inspiré par son illustre prédécesseur à la faculté de Pise, Galileo Galilei, notre lauréat 92, Clodoveo Ferri, a reçu, au pied de la tour penchée, l'illumination qui devait le conduire à démontrer définitivement le rôle



du virus de l'hépatite C dans les cryoglobulinémies mixtes essentielles. Si cette découverte, qui dispense quelques lumières sur une pathologie "froide", ne justifiait pas le bûcher, elle valait bien un laurier.

Professeur associé de rhumatologie à l'Institut de Pathologie Médicale I de l'université de Pise, dans l'unité de rhumatologie et d'immunologie clinique, Clodoveo Ferri suspectait depuis longtemps le rôle étiologique possible d'un virus hépatotrope dans les cryoglobulinémies mixtes essentielles (CGME). Plusieurs équipes avaient en effet noté l'existence de perturbations hépatiques au cours des CGME : hépatomégalie, exceptionnellement syndromes cliniques d'hypertension portale ou d'insuffisance hépatocellulaire, ou plus souvent simples anomalies biologiques.

Cependant le premier agent incriminé, à savoir le virus de l'hépatite B, ne s'est pas révélé particulièrement coupable : le virus n'était pas retrouvé de façon constante et l'A_gHBs n'était détecté que dans un petit nombre de cas.

Un virus sous surveillance

Lorsqu'en 1989, le virus de l'hépatite C, représentant 80 à 90 % des hépatites non A non B, a enfin pu être

mis en évidence, par des chercheurs du CDC d'Atlanta et de la firme Chiron, après 9 ans de recherche acharnée, le Pr Ferri s'est certainement frotté les mains, pressentant là un nouveau champ d'exploration. De fait, un an seulement après l'isolement du matériel génétique du virus de l'hépatite C (VHC) par Q.L. Choo et coll., C. Ferri présentait des résultats préliminaires concernant l'association possible entre ce virus et les CGM.

Dans le même temps, d'autres équipes pistaient également le VHC au tréfonds des cryoglobulinémies mais c'est notre lauréat qui, en 1991, a publié la première grande série mettant en évidence des anticorps anti-VHC, au moyen d'un test de première génération, dans 22 des 40 cas de CGM essentielle étudiés dans son service alors que les 55 malades présentant une pathologie dysimmunitaire (20 polyarthrites rhumatoïdes, 20 lupus et 15 syndromes de Gougerot-Sjögren) étaient tous seronegatifs.

Des gènes dans le sérum

Un peu plus tard, C. Ferri a repris l'étude de 52 patients porteurs d'une CGM (23 de types II et 29 de type III), en excluant les sujets ayant des facteurs de risque pour le virus de l'hépatite C. Cette fois-ci, la recherche d'anticorps a été réalisée au moyen d'un test ELISA de première génération et d'un test RIBA de deuxième génération.

Là encore une sérologie positive pour le VHC était associée à la CGME dans près de 60 % des cas. Un lien net avec une hépatite histologique et l'hypertransaminasémie a également pu être noté. De plus, le cryoprécipité contenait dans 25 % des anticorps dirigés contre le VHC.

Ces résultats ont été largement confirmés par d'autres auteurs et par C. Ferri lui-même : en utilisant des tests de deuxième génération, une positivité sérologique a été constatée dans 90 % des cas sur 42 CGME étudiées et surtout, la PCR était positive dans 86 % des observations, que les patients aient ou non une hépatite.

ABSTRACTISSIME 92



Les Best d'Abstract Rhumato (p. 7).

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Q uatre-vingt-treize.
Est-ce une révolte décrite par une plume hugolienne ? Non, lecteurs, c'est une révolution (terrestre !). La prochaine.
Abstract Rhumato s'y prépare, jetant ses troupes les plus valeureuses dans le dernier combat de 1992, le quatre-vingt-quatorzième depuis qu'il va au feu. Clodoveo Ferri a été désigné pour partir en éclaireur. On ne pouvait mieux choisir que ce condottiere pisan pour débusquer le virus de l'hépatite C camouflé dans le maquis des cryoglobulinémies (Le Lauréat, page 5). Mais voici en seconde ligne les meilleurs du bataillon d'articles, de ceux qu'on distingue et qu'on décore de lauriers pour avoir au milieu de tant d'autres papiers mené la charge d'Abstract Rhumato pendant toute cette année que nous disions presque révolue (Les Best, page 7).

Mais où en sont les alliés ?

C'est-à-dire les rhumatologues du reste de l'Europe...

Qu'on ne s'y trompe pas ! Ici ou de l'autre côté des ci-devant frontières, c'est le même combat (Rhumato sans frontières, page 14).

Plus loin, les autres corps d'armée (cardiologues, neurologues, psychiatres, gastro-entérologues, pédiatres, dermatologues, gynécologues...) se sont réunis pour parler de la stratégie de leurs propres combats.

Faites circuler le mot de passe (Médicoscopie, page 22)...

Cependant, les négociations se poursuivent à l'arrière.

Vérifiant plus que jamais l'adage "la guerre est décidée par ceux qui ne la font pas", ministres de la santé, directeurs de caisse et présidents des syndicats professionnels en sont encore aux Grandes Manœuvres malgré plusieurs plans de batailles successivement avalisés puis rejetés.

Il n'y aura pas en 92 de Convention nationale... nonobstant les accords historiques (Profession santé, page 27).

Bref, il n'est que temps de nous accorder une trêve.

Celle de Noël par exemple.

Marie-Line Barbet



Si ces résultats se trouvent confirmés, le nombre des CGM dites essentielles devrait donc singulièrement diminuer. Reste que les mécanismes physiopathologiques qui pourraient expliquer la relation entre VHC et CGME ne sont pas encore totalement éclaircis. Selon notre chercheur italien "le VHC, mais également à un moindre degré le VHB ou d'autres virus inconnus, pourrait provoquer un trouble lymphoprolifératif

responsable de la production de facteur rhumatoïde et de taux élevés de complexes immuns circulants (CIC) incluant les cryoglobulines, ces dernières étant responsables de lésions vasculaires à l'origine des différentes manifestations cliniques". De plus, "une altération de la clairance des CIC par les cellules de Kuppfer peut contribuer à maintenir des taux sériques élevés de cryoglobulines potentiellement toxiques".

Pour l'instant il est cependant impossible à C. Ferri de confirmer la possible séquence : infection par le VHC - hépatite chronique - cryoglobulinémie. Mais il précise cependant que "le suivi de plus de 200 cas de CGM montre que pour 20 % des dossiers, l'hépatite précède les manifestations typiques de la CGM (purpura, asthénie, arthralgies, neuropathie périphérique, néphropathie, ulcérations cutanées). Dans 48 % des observations, l'hépatite apparaît au cours de l'évolution de la maladie alors que dans 32 % des cas, une atteinte clinique hépatique manifeste n'est pas détectable ; la prévalence du VHC étant dans ce dernier cas comparable à celle observée pour la totalité des CGM".

Cependant la plupart des études réalisées incluaient de nombreux patients porteurs d'anomalies hépatiques. Y aurait-il là un biais ? Apparemment pas pour notre rhumatologue pisan qui avance que "la même prévalence des marqueurs du VHC constatée dans le groupe des patients n'ayant aucun signe clinique ni sérologique d'hépatite indique clairement que le VHC, qui est un virus à la fois hépatotrope et lymphotrope, est responsable de perturbations immunologiques plus complexes".

Plus encore, une fréquence élevée d'infection par le VHC ayant été rapportée dans les hépatites chroniques auto-immunes, C. Ferri et ses collaborateurs font l'hypothèse d'un mécanisme étiopathogénique commun aux CGM et aux hépatites chroniques auto-immunes.



Clodoveo Ferri, chercheur chaleureux pour une affection froide.

Un traitement à l'épreuve

Plusieurs équipes ont tenté de traiter les CGME par interféron (IFN) alpha avec un certain succès. C. Ferri propose cette modalité thérapeutique chez les patients ayant une infection à VHC manifeste et une maladie active, en général avec vascularite cutanée et hépatite.

De plus, il propose "une personnalisation des modalités thérapeutiques, à savoir de la dose et de la durée du traitement, suivie par une diminution lente de l'IFN alpha afin d'éviter un phénomène de rebond, un critère d'exclusion important étant la présence d'une neuropathie périphérique sévère".

Les jours prochains seront donc encore laborieux pour ce clinicien infatigable, mais on peut l'espérer, riches en découvertes. Décidés à mieux cerner le rôle du VHC dans la CGM et les relations entre l'hépatite des CGM et l'hépatite chronique auto-immune, C. Ferri et son équipe aimeraient aussi étudier les possibilités d'évolution des CGM en lymphome malin et le rôle de l'infection par le VHC dans ce phénomène.

Patricia Thelliez

Gros plan sur les cryo

Les cryoglobulines (GC) sont des immunoglobulines qui précipitent au froid et se redissolvent à 37 °C.

On distingue :

- Des CG monoclonales (type I) qui sont formées d'un composant monoclonal, le plus souvent IgM.

- Des CG mixtes à composant monoclonal (type II) qui correspondent à des complexes immuns comprenant une immunoglobuline monoclonale (le plus souvent une IgM) et une immunoglobuline polyclonale, généralement une IgG, le premier constituant exerçant une activité rhumatoïde ou anti-idiotypique contre le second.

- Des CG mixtes polyclonales (type III) constituées d'immunoglobulines polyclonales comprenant, le plus souvent, une IgM polyclonale à activité anti-IgG (facteur rhumatoïde).

Les CG de type I sont responsables des tableaux les plus sévères liés à l'hyperviscosité plasmatique et/ou à leur précipitation intravasculaire. Les CG mixtes, surtout de type II, provoquent une vascularite par dépôt de complexes immuns circulants avec classiquement asthénie, arthralgies, purpura et parfois anomalies hépatiques. Les CG mixtes de type III sont souvent asymptomatiques.

Les causes des CG sont multiples. Les CG monoclonales sont surtout observées au cours des lymphomes et des hémopathies. Les CG mixtes sont essentiellement constatées au cours d'affections auto-immunes ou infectieuses. Dans 18 à 30 % des cas, aucune cause ne peut être retenue : la CG est dite essentielle.



EUROPEAN SOCIETY OF PATHOLOGY



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5 February 1997

Professor Clodovco Ferri
Istituto de Patologia Medica 1
Universita of Pisa
Via Roma 67
5600 Pisa, Italia
Fax :00 39 50 550582

Dear Professor Ferri

553 632

Many thanks for your letter dated January 3. I really enjoyed reading your recent publications.
I am also very impressed by the tremendous activity of your group.

You have no idea how pleased I am to find beautifully demonstrated in a modern and sophisticated way, the hypothesis which we crudely ventured more than twenty years ago.
Anecdotally, I remember the kind words which an oncologist at the Cancer Institute, seated behind me during a CPC, whispered in my ear : « Heimann, avec tes cirrhoses et lymphomes, tu racontes des conneries ! »
I am also impressed by the fact that the concept that some lymphoproliferative disorders could be related to Hepatitis C has been developed essentially if not exclusively in Italy.

I just came back from a haematopathology course in San Diego, California where among others, I met Nancy Harris, one of the teachers and who is a well known haematopathologist at the Mass. General Hospital in Boston. I know her for many years. She was aware of our respective works and as matter of fact she alludes to the paper of Pozzato et al. (Blood 1994) in her chapter on low grade B-cell lymphomas in the recent (1996) monography on pathology of the lymphnodes edited by Lawrence Weiss and published by Churchill Livingstone.

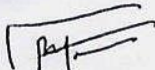
So slowly but surely the concept that hepatitis viruses can induce lymphoproliferative disorders is gaining acceptance in the haematopathologists' community !

I thank you very much also for the offer to collaborate with you. Actually, I was chairman of the Department of Pathology at the Institut Jules Bordet until my retirement in October 1995 ; I am now consultant at the Department of Pathology of the Flemish Medical School and Academic Hospital ; I shall hold this full-time position until end of March and from then on, I shall remain consultant on a part-time basis. So I shall have plenty of time then. I would be delighted to collaborate with your team and would like to discuss with you how this could be done. Maybe we could meet for instance sometime in this coming spring or early summer at your best convenience ?.

In fact, my wife and I had planned to drive down to Rome and visit some close friends there. The date is still open and I would not mind taking the opportunity to visit you in Pisa. If you wish, I could even give a talk on the historical steps of our understanding of the relationship between liver diseases and lymphoproliferative disorders.

Looking forward to hearing from you and with my best regards, I am,

Yours sincerely,


R. Heimann

PS. I did not succeed
in sending you this
letter as a fax.

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