Rheumatol Int (1999) 18: 171–176

ORIGINAL ARTICLE

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Agalactosyl IgG is elevated in patients with active spondyloarthropathy

Received: 9 July 1998 / Accepted: 14 January 1999

Abstract Patients with rheumatoid arthritis or with Crohn's disease have deficient galactosylation of serum IgG [Gal (0)]. To study whether such deviation occurs in patients with spondyloarthropathy (SPA), we studied the percentage incidence of Gal (0) corrected for age [Gal $(0)_{corr}$] in 47 SPA patients undergoing ileocolonoscopy and correlated the findings with clinical variables and prognosis of the patients. Gal $(0)_{corr}$ was elevated in 36% of the patients. Such patients had a higher number of inflamed joints ($P < 0.02$), higher ESR ($P < 0.001$) and CRP ($P < 0.001$). Elevated Gal $(0)_{corr}$ was also of prognostic significance: at 6-month follow-up those with elevated levels had a higher number of inflamed joints ($P < 0.02$) and ESR ($P < 0.05$). The presence of high Gal $(0)_{corr}$ did not associate with gut inflammation. In conclusion, a proportion of SPA patients has elevated levels of Gal (0), the amount of which correlates with severity of the disease and is a prognostic marker for chronicity of the disease.

Key words Agalactosylated IgG · Spondyloarthropathy · Reactive arthritis · Ankylosing spondylitis

Introduction

The proportion of oligosaccharide side chains of immunoglobulin G bearing no galactose [agalactosyl IgG (Gal (0)] in the Fc region and terminating in N-acetyl glucosamine (GlcNAc) is increased in the sera of patients with rheumatoid arthritis (RA) [1], inflammatory bowel disease, especially in patients with active Crohn's disease [2, 3], or with infection due to *Mycobacterium tuberculosis* [3]. In RA patients, the amount of Gal (0) is a good marker for active disease [4] and has a prognostic significance, patients with progressive disease having higher levels [5, 6, 7].

The putative mechanisms of agalactosylation of IgG are still not completely known. This has been mainly discussed in association with RA. B cells from RA patients have reduced galactosyltransferase activity [8] which is reflected in the increased production of agalactosylated IgG [9]. Cytokines and oxygen radicals have been suggested to contribute to the agalactosylation [10]. Alterations in interleukin (IL)-6 production in patients with RA have been associated with high agalactosyl IgG levels [11]. However, no association has been found between the levels of Gal (0) and IL-6 or soluble IL-2 receptor levels in the sera of RA patients [12].

The changes in glycosylation can result in a reduced ability of IgG to bind to Fc gamma receptors of polymorphonuclear leukocytes [13], and impair the fixing of complement, the participation in antibody dependent cytotoxicity, the binding to macrophages, and the elimination of antigen-antibody complexes, as discussed by Axford [14]. The terminal GlcNAc has been shown to bind to the collagenous lectin mannose-binding protein (MBP), which can result in the activation of the complement [15]. The abnormalities described above have been associated with the pathogenesis of RA but not with that of seronegative spondyloarthropathy (SPA). However, the presence of bacterial-antibody complexes is observed in reactive arthritis [16] and impaired antigen elimination has also been suggested to play a role in the pathogenesis of SPA [17].

Infection through mucosal route and/or gut inflammation, permitting the entry of potential enteric pathogens into the host, plays a role in the pathogenesis of reactive arthritis and SPA [18]. A high frequency of silent gut inflammation, occasionally resembling lesions in Crohn's disease, has been observed in patients with SPA [19, 20]. Because of the associations between Gal (0) and Crohn's disease, we studied the presence and the level of Gal (0) in the sera of patients with various types of SPA and correlated the results with clinical features, laboratory markers of inflammation, gut findings, and the later prognosis of the patients.

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Table 1 Patients and controls

	Enteroarthritis		Uroarthritis		Chronic oligo-/poly-arthritis	Sacroiliitis/ ankylosing spondylitis	Total	Controls	
	Acute ($n=10$)	Chronic ($n=1$)	Acute ($n=2$)	Chronic ($n=2$)	($n=11$)	($n=21$)	($n=47$)	RA ($n=4$)	Other ($n=11$)
Sex (M/F)	3/7	0/1	2/0	2/0	2/9	13/8	22/25	0/4	2/9
Age, years, mean (SD)	38.2 (16.2)	36.0 (–)	22.0 (–)	26.5 (–)	34.1 (9.4)	35.8 (8.6)	34.9 (10.8)	48.5 (14.2)	36.5 (11.6)
Sacroiliitis	2/10	1/1	0/2	2/2	1/11	19/21	25/47	0/4	3/11
Gut inflammation									
Endoscopic	6/10	1/1	1/2	0/2	2/11	12/21	22/47	0/4	3/11
Histologic	5/10	0/1	1/2	1/2	2/11	7/21	16/47	2/4	3/11
Increased Gal $(0)_{corr}$	5/10	0/1	1/2	0/2	4/11	7/21	17/47	3/4	1/11
Gal $(0)_{corr}$, %, median (range)	10.9 (–7.0, +17.9	–7.9 (–)	15.4 (+7.3, +23.5)	–3.3 (–9.0, +2.3)	4.2 (–6.8, +20.8)	4.9 (–19.4, +25.6)	4.9 (19.3, +25.6)	15.1 (–13.1, +23.7)	1.1 (–13.2, +13.4)

Patients and methods

Patients

Sera from 47 patients with SPA, belonging to a study in which ileocolonoscopy was performed in a search for asymptomatic gut inflammation [20], were analyzed for Gal (0). The patients included 15 patients with reactive arthritis, 11 with chronic seronegative oligo- or polyarthritis, and 21 with sacroiliitis or ankylosing spondylitis. Reactive arthritis was diagnosed as described previously [21]. In 11 patients, the arthritis was triggered by gut infection (enteroarthritis; 5 with *Yersinia enterocolitica*, 3 with *Salmonella*, 1 with *Shigella flexneri*, 1 with *Staphylococcus aureus* enteritis, and 1 patient with diarrhea of unknown etiology). In 4 patients, reactive arthritis was triggered by urethritis (uroarthritis; 2 patients with *Chlamydia trachomatis*, 2 patients with nonspecific urethritis). Chronicity was defined as the duration of arthritis for ≥6 months. Patients with seronegative oligo- or polyarthritis fulfilled the European Spondylarthropathy Study Group (ESSG) criteria for spondylarthropathy [22], and patients with ankylosing spondylitis fulfilled the New York diagnostic criteria [23]. Patients with radiologic evidence of only unilateral sacroiliitis, with or without peripheral arthritis, were grouped under the diagnosis of sacroiliitis. The patients were treated at the out-patient department of the Helsinki University Central Hospital. The initial Gal $(0)_{corr}$ levels studied at the time of ileocolonoscopy (i.e., at entry) were correlated with the clinical features at 6 and 12 months later, and with laboratory tests measuring inflammation (erythrocyte sedimentation rate, ESR, and C-reactive protein, CRP) at 3, 6 and 12 months later.

Sera from an additional 15 control subjects also undergoing ileocolonoscopy were analyzed for the Gal (0) levels. There were 4 patients with RA, 3 with uncomplicated bacterial gastroenteritis, 2 patients with noninflammatory back pain, and 6 patients with miscellaneous rheumatic symptoms (1 with Sjögren's syndrome, 1 with joint symptoms in association with celiac disease, 2 patients with arthritis in association with sore throat, 1 patient with fibromyalgia, and 1 patient with arthralgia).

The study was approved by the local ethical committee, and the patients gave their informed consent before the study.

Methods

The study sera were collected at the time of ileocolonoscopy and were kept at –20 °C until analyzed as coded samples by coworkers with no access to the clinical data. As there is an increase in the level of Gal (0) with increasing age [10], age-corrected Gal (0) [Gal $(0)_{corr}$] values were obtained by subtracting the mean value found in normal control individuals of the same age [10] from the actual Gal (0) value. Mean + 2 SD of Gal $(0)_{corr}$ is regarded as the cut-off point for the upper limit of normal.

The percentage incidence of Gal (0) in the sera obtained from the patients was determined by solid phase immunoassay using a monoclonal antibody (GN7) to GlcNAc as described previously [24]. Briefly, sera were diluted 1 : 100 and added to ELISA plates precoated with a fixed concentration of protein A. This provided an excess of IgG so that all wells contained the same quantity. The IgG was then denatured by heating the plates at 85 °C for 8 min, in order to expose the oligosaccharides on the Fc region. The binding of GN7 to terminal GlcNAc was then determined as described [24], and converted into Gal (0) using a standard curve run on the same plates. The standards used to generate this curve were sera in which the Gal (0) had been predetermined by a precise biochemical method [1]. These standards were provided by Prof. T. W. Rademacher, Molecular Medicine Unit, Department of Molecular Pathology, UCL Medical School, London. The method used for the standards involves cleaving the oligosaccharides from highly purified IgG using hydrazinolysis. The oligosaccharides are then radiolabelled, and digested with a mixture of exoglycosidases that result in large hydrodynamic volume differences between oligosaccharides that bear none, one or two Galβ1-4G1cNAc structures. These are then resolved by Biogel P4 gel permeation chromatography [25].

Statistical treatment

The associations between the presence or absence of elevated levels of Gal $(0)_{corr}$ and the presence of clinical features in the patients were calculated with χ^2 test (with Yates' correction when appropriate). Comparisons of the levels of Gal $(0)_{corr}$ between patient groups were analyzed by Mann-Whitney U-test, and correlations between the level of Gal $(0)_{corr}$ and the number of inflamed joints, and laboratory markers of inflammation by the Spearman correlation coefficient *r*.

Results

The clinical features of the patients with Gal $(0)_{corr}$ in different patient groups are presented in Table 1. Gal $(0)_{corr}$ was increased in 36% of the SPA patients. There were no statistically significant differences in the frequencies of increased Gal $(0)_{corr}$ between the subgroups of patients. The median level of Gal $(0)_{corr}$ in the patients did not differ significantly from that in the control subjects with RA, but tended to be higher than that of the controls with miscel-

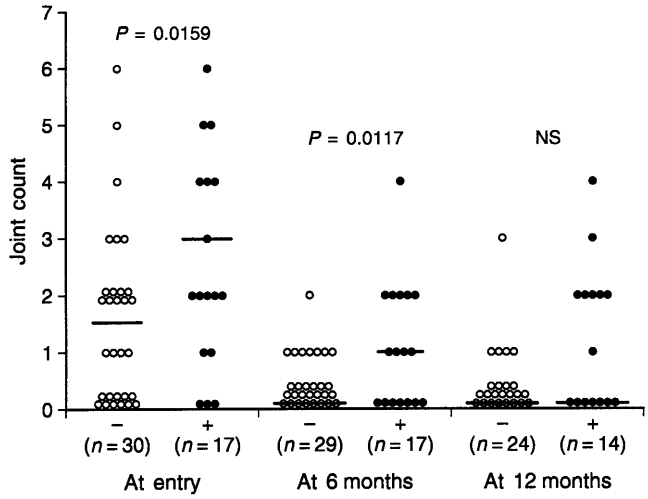

Fig. 1 Joint counts in patients with spondyloarthropathies according to normal (○) or increased (●) levels of age-corrected agalactosyl IgG, Gal $(0)_{corr}$. Horizontal line denotes median

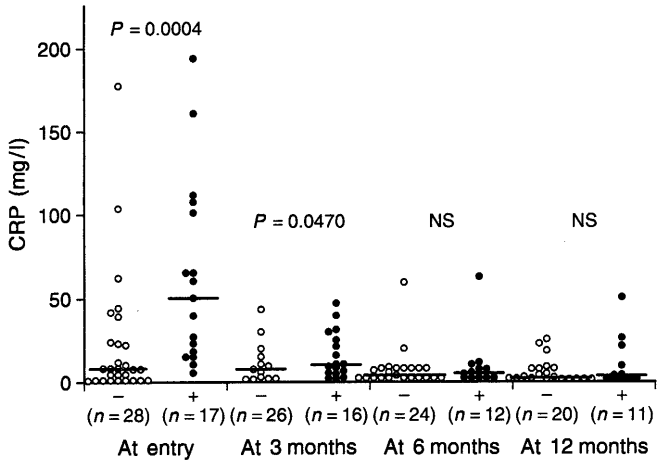

Fig. 3 C-reactive protein (CRP) levels in patients with spondyloarthropathies according to normal (○) or increased (●) levels of Gal $(0)_{corr}$. Horizontal line denotes median

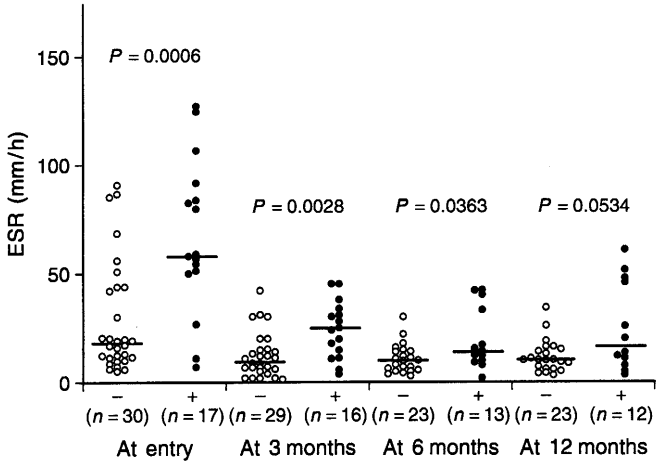

Fig. 2 Erythrocyte sedimentation rate (ESR) in patients with spondyloarthropathies according to normal (○) or increased (●) levels of Gal $(0)_{corr}$. Horizontal line denotes median

laneous symptoms ($P=0.062$). The levels of Gal $(0)_{corr}$ in patients with acute reactive arthritis (median 10.9, range −7.0−23.5) did not differ significantly from those in the control subjects with rheumatoid arthritis (15.1, range −13.1−25.6) (Table 1).

At the time of ileocolonoscopy (i.e., at entry in the prospective study), patients with increased Gal $(0)_{corr}$ had a higher number of affected peripheral joints (Fig. 1), ESR (Fig. 2) and CRP (Fig. 3). Gal $(0)_{corr}$ also predicted persistence of joint symptoms: those with increased Gal $(0)_{corr}$ at entry had a higher number of inflamed joints at 6-month follow-up (Fig. 1). Also, increased Gal $(0)_{corr}$ at entry predicted prolonged inflammation as measured by ESR (Fig. 2), and less distinctly by CRP, during the subsequent 1-year follow-up (Fig. 3).

Frequency of increased Gal $(0)_{corr}$ did not differ between patients with respect to the presence or absence of peripheral arthritis or gut symptoms (data not shown) or symptoms of sacroiliitis, gender, HLA-B27, or endoscopic or histologic findings at endoscopy (Table 2).

Table 2 Comparison between patients with normal and elevated levels of agalactosylated IgG at entry

	Level of agalactosylated IgG		*P*
	Normal	Increased	
Gut inflammation			
Endoscopic (%)	40	59	NS
Histologic (%)	30	41	NS
Symptomatic sacroiliitis (%)	60	41	NS
Presence of HLA-B27 (%)	90	82	NS
Gender (M/F)	11/19	11/6	NS

The levels of Gal $(0)_{corr}$ at entry correlated with ESR initially ($r=0.49$, $P<0.001$; Fig. 4), at 3-month ($r=0.50$, $P<0.001$), at 6-month ($r=0.34$, $P<0.05$) and at 12-month follow-up ($r=0.32$, $P<0.05$). Similar correlations were observed between Gal $(0)_{corr}$ and CRP initially ($r=0.57$, $P<0.001$) (Fig. 5) and at 3-month follow-up ($r=0.40$, $P<0.01$).

The level of Gal $(0)_{corr}$ did not differ significantly between HLA-B27 positive and negative patients, presence or absence of peripheral arthritis or sacroiliitis, or with respect to endoscopic or histological gut inflammation (data not shown).

Discussion

We observed an increased prevalence of agalactosyl IgG in patients with SPA. Patients with acute reactive arthritis had the highest levels, reaching the levels observed in RA.

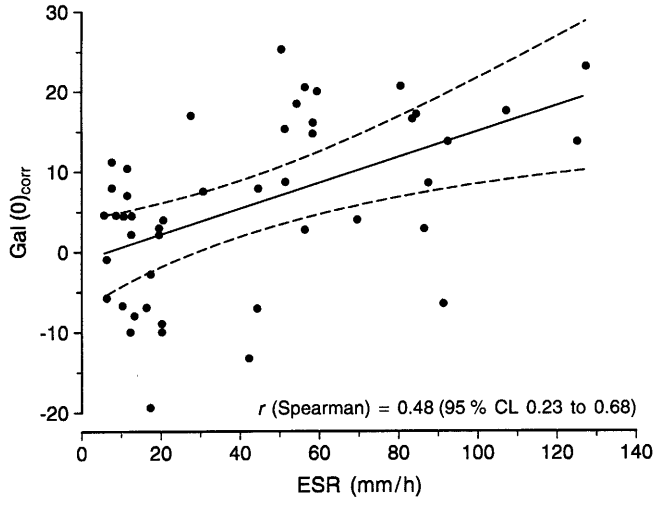

Fig. 4 Correlation between $Gal(0)_{corr}$ and ESR in patients with spondyloarthropathy at entry

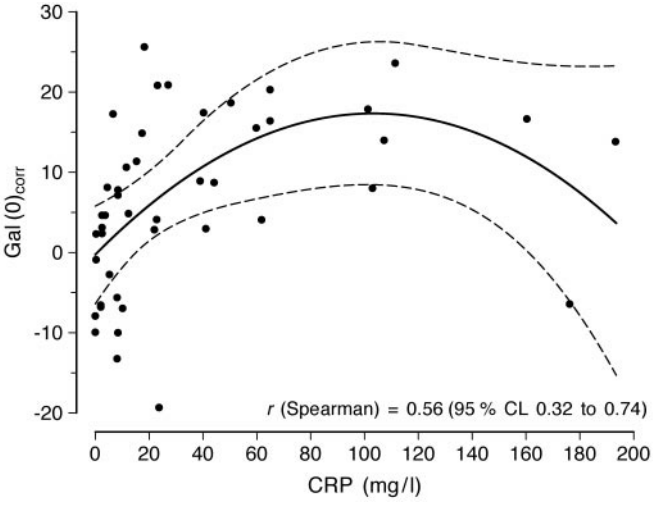

Fig. 5 Correlation between $Gal(0)_{corr}$ and CRP in patients with spondyloarthropathy at entry

Both the presence and the level of $Gal(0)_{corr}$ were associated with the number of peripheral joints involved and with markers of inflammation. The initial level of $Gal(0)_{corr}$ also served as a prognostic marker for chronic inflammation during the subsequent year. Our finding differs from a previous study [3], in which 12 patients with seronegative arthropathies and 10 patients with Yersinia-induced arthritis were tested. However, the limited number of patients and lack of clinical data in the report of Parekh et al. [3] do not allow further comparisons between their results and those reported here.

Half of our patients had macroscopic and/or histologic inflammation in the gut. The presence of such lesions was not reflected in the increased prevalence or levels of $Gal(0)_{corr}$. This is contrary to the findings reported for inflammatory bowel disease [2, 26]. The gut lesions in SPA can be acute or chronic, and the acute lesions are interpreted to be associated with possible gut infection [19]. A subset of chronic lesions resemble early lesions of Crohn's disease [20]. By ileocolonoscopy, it is possible to visualize the whole colon, but only a small part of the ileum. Although there is less knowledge of the extent of the lesions in the small bowel, previous studies [27] have shown that half of the SPA patients have lesions in the colon. Also, the lesions in SPA are small and patchy and do not involve the whole gut. Evidently, such lesions do not evoke a systemic inflammatory response which is reflected in the levels of $Gal(0)_{corr}$.

We observed increased levels of N-acetylglucosamine indicating agalactosylation of IgG in our patients. However, we cannot be sure that the glycosylation change we detected in SPA is the same as previously detected in patients with RA. A variety of oligosaccharide structures has been shown to exist on this conserved glucosylation site of the Fc portion of IgG [1]. They can vary in the presence or absence of a bisecting GlcNAc, or of additional fucosylation. All that we can state is that in the diseases studied (SPA and RA) there is an increase of oligosaccharides which have terminal GlcNAc, and that they are situated on the conserved glycosylation site of asparagine 297 of the Fc. This location is extremely probable because the antibody does not bind to IgG from patients with either diseases unless the IgG has been heat denaturated (data not shown). This is characteristic of the oligosaccharides in this position, because they point inward towards the center of the doughnut-like structure formed by the heavy chains of IgG. Oligosaccharides at other sites on IgG are accessible to antibodies without denaturation. Moreover, any IgG with terminal mannose of GlcNAc on the Fab is removed rapidly from the circulation by sugar receptors in the liver and on macrophages. However, terminal GlcNAc on the sugars in the Fc portion of IgG does not result in removal from the circulation, because of its concealed location within the "doughnut" [28].

The proportion of SPA patients with increased $Gal(0)_{corr}$ in the present study (36%) is comparable to that observed in RA (20–40%) [4]. The levels of $Gal(0)_{corr}$ in most patients with SPA were, however, lower than in the control RA patients in the present study. Analogous to studies on RA [4, 6], a high percentage of agalactosylation correlated with disease activity and prognosis. Thus, our results show that, although initially associated with active RA, agalactosylated IgG is also a marker of active inflammation in other forms of rheumatic disease. High Gal(0) has been observed in patients with Takayasu's arteritis [29] or with systemic lupus erythematosus [30]. Thus, the demonstration of a raised level of Gal(0) in a patient with early synovitis warrants differential diagnostic studies, and cannot be interpreted as a sign of RA, as suggested previously [30].

The pathogenetic role of Gal(0) is still incompletely known. It is also not known whether increased Gal(0) represents decreased galactosylation of all IgG, or an increase in the relative concentration of a subset of agalactosyl antibodies with specificity relevant to the disease process. A recent study showed that specific pathogen free CBA/Ca

mice, when transferred from a sterile to a conventional environment, had an increase of total serum IgG whereas the degree of galactosylation of IgG fell [31].

Thus, the galactosylation of IgG varies during the development of normal immune response. Agalactosylated IgG may not itself be of pathogenetic significance, unless the antibody has specificity. Animal studies speak for the pathogenetic role of agalactosylated IgG in arthritis. Passive transfer of an acute synovitis in T cell-primed mice can be enhanced by using IgG-containing autoantibodies to collagen II when the antibodies are presented as the agalactosyl glycoforms [32]. In patients with SLE, low concentrations of Gal (0) during pregnancy seem to be pathogenic for the fetus. Maternal-fetal transmission of Gal (0) antibodies with specificity to Ro (SS-A) or La (SS-B) has been recently associated with the development of congenital heart block [33]. The possible role of agalactosyl IgG is not known in SPA, a heterogenic group of diseases, the pathogenesis of which is still incompletely understood. The determination of the specificity of antibodies of the agalactosyl IgG class will perhaps in the future aid in the definition of the antigen(s) contributing to the development of SPA.

In conclusion, agalactosylation of IgG occurs in SPA. In addition, the level of Gal $(0)_{corr}$ correlates with the number of inflamed joints and with laboratory markers of inflammation. The level also has prognostic importance. Sulfasalazine is effective in SPA [34]. During sulfasalazine treatment of RA patients, lymphocyte galactosyltransferase activity and Gal $(0)_{corr}$ return to normal [35]. We can only speculate as to whether the level of Gal $(0)_{corr}$ can be used to monitor therapeutic response in patients with SPA.

Acknowledgements We are grateful to Mr. H. Kautiainen for the statistical consultations. This work was supported by grants from the Paulo Foundation, Helsinki, the Rheumatism Research Foundation, Helsinki, the Finnish Cultural Fund, the Yrjö Jahnsson Foundation, and the Academy of Finland.

References

1. Parekh RB, Dwek RA, Sutton BJ, Fernandes DL, Leung A, Stanworth D, Rademacher TW, Mizuochi T, Taniguchi T, Matsuta K, Takeuchi F, Nagano Y, Miyamoto T, Kobata A (1985) Association of rheumatoid arthritis and primary osteoarthritis with changes in the glycosylation pattern of total serum IgG. Nature 316: 452–457
2. Dubé R, Rook GAW, Steele J, Brealey R, Dwek R, Rademacher T, Lennard-Jones J (1990) Agalactosyl IgG in inflammatory bowel disease: correlation with C-reactive protein. Gut 31: 431–434
3. Parekh R, Isenberg D, Rook G, Roitt I, Dwek R, Rademacher T (1989) A comparative analysis of disease-associated changes in the galactosylation of serum IgG. J Autoimmun 2: 101–114
4. Parekh RB, Roitt IM, Isenberg DA, Dwek RA, Ansell BM, Rademacher TW (1988) Galactosylation of IgG associated oligosaccharides: reduction in patients with adult and juvenile onset rheumatoid arthritis and relation to disease activity. Lancet 1: 966–969
5. Zeben D van, Hazes JMW, Zwinderman AH, Vandenbroucke JP, Breedveld FC (1993) Factors predicting outcome of rheumatoid arthritis: results of a follow-up study. J Rheumatol 20: 1288– 1296
6. Zeben D van, Rook GAW, Hazes JMW, Zwinderman AH, Zhang Y, Ghelani S, Rademacher TW, Breedveld FC (1994) Early agalactosylation of IgG is associated with a more progressive disease course in patients with rheumatoid arthritis: results of a follow-up study. Br J Rheumatol 33: 36–43
7. Bodman-Smith K, Sumar N, Sinclair H, Roitt I, Isenberg D, Young A (1996) Agalactosyl IgG [Gal (0)] – an analysis of its clinical utility in the long-term follow-up of patients with rheumatoid arthritis. Br J Rheumatol 35: 1063–1066
8. Axford JS, Lydyard PM, Isenberg DA, Mackenzie L, Hay FC, Roitt IM (1987) Reduced B cell galactosyltransferase activity in rheumatoid arthritis. Lancet 2: 1486–1488
9. Bodman KB, Sumar N, Mackenzie LE, Isenberg DA, Hay FC, Roitt IM, Lydyard PM (1992) Lymphocytes from patients with rheumatoid arthritis produce agalactosylated IgG in vitro. Clin Exp Immunol 88: 420–423
10. Parekh R, Isenberg D, Roitt I, Dwek R, Rademacher T (1988) Age-related galactosylation of the N-linked oligosaccharides of human serum IgG. J Exp Med 167: 1731–1736
11. Rademacher TW, Jones RHV, Williams PJ (1995) Significance and molecular basis for IgG glycosylation changes in rheumatoid arthritis. Adv Exp Med Biol 376: 193–204
12. Bond A, Sumar N, Bodman K, Colaco CB, Young A, Hay FC (1994) Relationship of IgG glycosylation, soluble IL-2 receptors and IL-6 to disease activity in rheumatoid arthritis. Br J Rheumatol 33: 992–993
13. Adler Y, Lamour A, Jamin C, Menez JF, Le Corre R, Shoenfeld Y, Youinou P (1995) Impaired binding capacity of asialyl and agalactosyl IgG to Fc gamma receptors. Clin Exp Rheumatol 13: 315–319
14. Axford JS (1991) Oligosaccharides: an optional extra or of relevance to disease mechanisms in rheumatology? J Rheumatol 18: 1124–1127
15. Malhotra R, Wormald MR, Rudd PM, Fischer PB, Dwek RA, Sim RB (1995) Glycosylation changes of IgG associated with rheumatoid arthritis can activate complement via the mannose-binding protein. Nat Med 1: 237–243
16. Lahesmaa-Rantala R, Granfors K, Toivanen A (1986) Detection of circulating Yersinia-immunoglobulin complexes by enzyme immunoassay (EIA). J Immunol Methods 89: 191–199
17. Sieper J, Braun J (1995) Pathogenesis of spondylarthropathies. Persistent bacterial antigen, autoimmunity, or both? Arthritis Rheum 38: 1547–1554
18. Märker-Hermann E, Höhler T (1998) Pathogenesis of human leukocyte antigen B27-positive arthritis: information from clinical materials. Rheum Dis Clin North Am 24: 865–881
19. Mielants H, Veys EM, Goemaere S, Goethals K, Cuvelier C, De Vos M (1991) Gut inflammation in the spondyloarthropathies: clinical, radiologic, biologic and genetic features in relation to the type of histology. A prospective study. J Rheumatol 18: 1542– 1551
20. Leirisalo-Repo M, Turunen U, Stenman S, Helenius P, Seppälä K (1994) High frequency of silent inflammatory bowel disease in spondylarthropathy. Arthritis Rheum 37: 23–31
21. Lauhio A, Leirisalo-Repo M, Lähdevirta J, Saikku P, Repo H (1991) Double-blind, placebo-controlled study of three-month treatment with lymecycline in reactive arthritis, with special reference to Chlamydia arthritis. Arthritis Rheum 34: 6–14
22. Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, Cats A, Olivieri I, Pasero G, Veys E, Zeidler H, the European Spondylarthropathy Study Group (1991) The European Spondylarthropathy study group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum 34: 1218–1227
23. Moll JMH, Wright V (1973) New York clinical criteria for ankylosing spondylitis. Ann Rheum Dis 32: 354–363
24. Wang Y, Rook GAW (1996) Analytical methods 3: monoclonal antibodies. In: Isenberg D, Rademacher TW (eds) Abnormalities of IgG glycosylation and immunological disorders. Wiley, Chichester, pp 89–99
25. Williams PJ (1996) Analytical methods 1: biochemical. In: Isenberg D, Rademacher TW (eds) Abnormalities of IgG glycosylation and immunological disorders. Wiley, Chichester, pp 45–64

26. Tomana M, Schrohenloher RE, Koopman WJ, Alarcón GS, Paul WA (1988) Abnormal glycosylation of serum IgG from patients with chronic inflammatory diseases. Arthritis Rheum 31:333–338
27. Leirisalo-Repo M, Repo H (1992) Gut and spondyloarthropathies. Rheum Dis Clin North Am 18:23–35
28. Rademacher TW, Jaques A, Williams PJ (1996) The defining characteristics of immunoglobulin glycosylation. In: Isenberg D, Rademacher TW (eds) Abnormalities of IgG glycosylation and immunological disorders. Wiley, Chichester, pp 1–44
29. Hernández-Pando R, Reyes P, Espitia C, Wang Y, Rook G, Mancilla R (1994) Raised agalactosyl IgG and antimycobacterial humoral immunity in Takayasu's arteritis. J Rheumatol 21:1870–1876
30. Young A, Sumar N, Bodman K, Goyal K, Sinclair H, Roitt I, Isenberg D (1991) Agalactosyl IgG: an aid to differential diagnosis in early synovitis. Arthritis Rheum 34:1425–1429
31. Lastra GC, Thompson SJ, Lemonidis AS, Elson CJ (1998) Changes in the galactose content of IgG during humoral immune responses. Autoimmunity 28:25–30
32. Rademacher TW, Williams P, Dwek RA (1994) Agalactosyl glycoforms of IgG autoantibodies are pathogenic. Proc Natl Acad Sci USA 91:6123–6127
33. Pilkington C, Taylor PV, Silverman E, Isenberg DA, Costello AM de L, Rook GWA (1996) Agalactosyl IgG and materno-fetal transmission of autoimmune neonatal lupus. Rheumatol Int 16:89–94
34. Dougados M, van der Linden S, Leirisalo-Repo M, Huitfeldt B, Juhlin R, Veys E, Zeidler H, Kvien TK, Olivieri I, Dijkmans B, Bertouch J, Brooks P, Edmonds J, Major G, Amor B, Calin A (1995) Sulfasalazine in the treatment of spondyloarthropathy. A randomized, multicenter, double-blind, placebo-controlled study. Arthritis Rheum 38:618–627
35. Axford JS, Sumar N, Alavi A, Isenberg DA, Young A, Bodman KB, Roitt IM (1992) Changes in normal glycosylation mechanisms in autoimmune rheumatic disease. J Clin Invest 89:1021–1031