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s kiDecember 12/05:

ANCA in Churg-Strauss Syndrome

Churg-Strauss syndrome (CSS) is a form of systemic necrotising vasculitis in which there is prominent lung involvement with severe asthma, eosinophilia, and granulomatous reactions. It is classified among the so-called ANCA-associated systemic vasculitides. However, the prevalence of ANCA in CSS varies widely and their clinical significance remains uncertain. The following study gives some new evidence on this issue:

> Sinico RA, Di Toma L, Maggiore U, Bottero A, et al. (2005)
> Prevalence and Clinical Significance of Antineutrophil Cytoplasmic Antibodies in Churg-Strauss Syndrome
> *Arthritis Rheum 52, 2926-2935*

93 unselected consecutive patients in whom CSS was diagnosed clinically were tested for the presence of ANCA at the time of diagnosis (before starting immunosuppressive treatment) by indirect immunofluorescence (IIF) and ELISAs for PR3 and MPO antibodies.

ANCA measured by IIF were present in 35 patients (37.6%) and MPO or PR3 antibodies measured by ELISA were present in 30 and 3 patients, respectively. Of the 35 ANCA-positive patients, 26 showed a pANCA pattern with specificity for MPO in 24 patients, while a cANCA pattern with specificity for PR3 was found in 3 patients. 2 pANCA-positive samples were negative by ELISA. Interestingly, 6 non-pANCA patterns (3 cANCA patterns and 3 atypical ANCA patterns) were found with anti-MPO antibodies by ELISA (confirmed by inhibition studies) being identified in each case.

ANCA positivity was associated with a significantly higher prevalence of renal involvement (51.4% versus 12.1% in ANCA-negative patients) and in particular with a clinical picture of rapidly progressive glomerulonephritis (28.6% versus 5.2%). ANCA-positive patients are more likely than ANCA-negative patients to present with the typical clinicopathologic picture of the other small-vessel vasculitides and are less likely to have heart and non-haemorrhagic lung involvement.

ANCA-positive patients tended to have a higher disease activity score (BVAS), but the difference was not statistically significant. Moreover, there was no statistical evidence that ANCA positivity carried a worse prognosis although the authors noted that ANCA positive patients were more likely to be treated with cyclophosphamide rather than just with corticosteroids. The risk of relapse at 5 years was 46.3% in ANCA-positive and 35.4% in ANCA-negative patients.

All patients were treated with corticosteroids and 37 were measured for ANCA at follow-up. ANCA were present in only 4 of these 37 patients (10.8%); however, one of these patients still had active disease. ANCA were present in 3 of 16 patients (18.8%) tested at the time of a relapse.

The prevalence of ANCA in this study is 37.6%, which corresponds to the majority of larger studies on ANCA in CSS and is clearly lower than in other ANCA associated vasculitides. Nevertheless, the measurement of ANCA is crucial and gives important information for diagnosis and clinical follow-up.

November 11/05:

Autoimmune disorders associated with celiac disease

Celiac disease is the most common hereditary gastroenterological disease. As can be read in the Publication of Month October 10/05, celiac disease has been found to be associated with type I diabetes. The following recent publication describes furthermore an association of celiac disease with other autoimmune diseases:

> Slate J, Hookman P, Barkin JS, Phillips RS (2005)
> Systemic Autoimmune Disorders Associated with Celiac Disease
> *Digestive Diseases and Sciences 50, 1705 – 1707*

This article presents a case report of a 50 years old woman with celiac disease, elevated liver enzyme tests and autoimmune hepatitis. This is the initial report of celiac disease associated with autoimmune hepatitis and HPG. However, it is known that a high percentage of patients with celiac disease show elevated liver transaminase levels. According to various studies, the percentage lies between 39 % and 54 %. About 95 % of these patients were shown to normalize on a gluten-free diet. This has not been reported to autoimmune hepatitis associated with celiac disease.

Based on this finding, the authors discuss the association of celiac disease with other autoimmune diseases. They cite a study that examined the prevalence of autoimmune diseases in celiac disease and found that the autoimmune disease was diagnosed in 114 of 147 cases (77.5 %) before the diagnosis of celiac disease was established. Multiple autoimmune disorders have been associated with celiac disease, including diabetes mellitus, type I dermatitis herpetiformis, connective tissue disease, autoimmune thyroid diseases, alopecia, psoriasis and Addison's disease. This may be explained by the sharing of common HLA class II alleles including B8, DQ2 and, most commonly, DR3. The frequency of celiac disease in patients with autoimmune diseases is unknown.

According to the authors, these results emphasize that patients with autoimmune diseases should also be evaluated for latent celiac disease.

October 10/05:

Autoantibodies in diabetic children

With the diagnosis of an autoimmune disease, the risk of acquiring other autoimmune disorders increases dramatically. In particular, children diagnosed with insulin-dependent diabetes mellitus (type 1 diabetes) are at high risk of developing an autoimmune thyroid disease or celiac disease, both belonging to the most frequent autoimmune diseases among children. In the following article, Glastras et al. aim to explore whether the presence of thyroid and endomysial antibodies at the time of diagnosis of type 1 diabetes in children predicts the development of thyroid and celiac disease, respectively and to determine the frequency with which screening for these associated diseases should be undertaken in these patients.

> Glastras SJ, Craig ME, Verge CF, Cusumano JM, Donaghue KC (2005)
> The Role of Autoimmunity at Diagnosis of Type 1 Diabetes in the Development of Thyroid and Celiac Disease and Microvascular Complications
> *Diabetes Care 28, 2170 – 2175*

Antibodies to thyroid peroxidase (anti-TPO) and endomysial antibodies (EMA) were measured at the time of diagnosis of type 1 diabetes in 166 children, aged 0-15 years. 13 children (7.8%) were positive for anti-TPO at that time. One girl was found to be hypothyroid at diagnosis and commenced thyroxin replacement therapy. Subsequent measurements of thyroid stimulating hormone (TSH) were made in the other 12 patients with positive anti-TPO and in 139 patients with negative anti-TPO. In addition to the girl who was directly diagnosed as having thyroid disease, 5 of 13 anti-TPO positive patients (46.2%) developed thyroid disease over the next 13 years, compared to only 5 of 139 children with negative anti-TPO (3.6%).

4 children (2.4%) were positive for EMA at the time of diagnosis. Within one year, celiac disease was confirmed in all 4 patients by small-bowel biopsy. 143 EMA-negative children were subsequently regularly screened for celiac disease. 4 of them (2.8%) seroconverted during the course of the follow-up for this study. Within 12 months of seroconversion, celiac disease was confirmed by small-bowel biopsy in all 4 patients, one of whom was also hypothyroid at the time of diagnosis of diabetes. Therefore, the prevalence of celiac disease in 166 diabetes patients was raised to 4.8%, which is about 5 times higher than in the normal population.

The authors conclude that both anti-TPO and EMA measured at the time of diagnosis were strong predictors of future thyroid and celiac disease, respectively. They recommend that all patients with type 1 diabetes should be screened for both thyroid and celiac disease at the time of diagnosis and at regular time intervals thereafter. Two-year intervals are appropriate in patients who have negative anti-TPO and EMA titres at the time of diagnosis of type 1 diabetes.

Since many publications have shown that good tTG antibody tests are equivalent to EMA one can recommend the same programme using anti-tTG instead of EMA (editor's comment).

September 09/05:

Infliximab induces ANA

Tumour necrosis factor (TNF) is a principal mediator in the host inflammatory response, particularly to bacteria. It is commonly expressed in the rheumatoid joint. In the 1990s, it was proven that the inhibition of TNF leads to a reduction of disease activity and joint inflammation in patients with rheumatoid arthritis (RA). TNF inhibitors used for treatment of RA are etanercept; a soluble TNF receptor, infliximab; a chimeric anti-TNF antibody, and adalimumab; a fully humanised monoclonal antibody.

It has been recognised for several years now that TNF blockers induce autoantibodies such as antinuclear antibodies (ANAs) and anti-double-stranded DNA (anti-dsDNA) antibodies. Nevertheless, the profound immunomodulation induced by blockers is associated with a relatively low incidence of immune-related complications such as demyelinating disease and lupus-like syndromes.

The authors of the present study analysed the clinical and biologic correlates of autoantibody induction during longer-term TNF blockade with either infliximab or etanercept.

> De Rycke L, Baeten D, Kruithof E, Van den Bosch F, Veys EM, De Keyser F (2005)
> Infliximab, but not Etanercept, induces IgM anti-double-stranded DNA autoantibodies as main antinuclear reactivity
> *J Rheumatol 32, 1267-1272*

A total of 113 patients with either spondylarthropathy (SpA) or RA were included in this study. 34 patients with SpA and 59 patients with RA were treated with infliximab for 2 years. 20 patients with SpA were treated with etanercept for 1 year.

High numbers of infliximab-treated patients with SpA or RA had newly induced IgG ANAs (61.8% and 40.7%, respectively) and anti-dsDNA antibodies (70.6% and 49.2%, respectively) after one year, but no further increase between year 1 and year 2 was observed. In contrast, induction of ANAs and anti-dsDNA antibodies was observed only occasionally in the etanercept-treated patients with SpA (10% of patients each). Isotyping revealed almost exclusively IgM or IgM/IgA anti-dsDNA antibodies, which disappeared upon interruption of treatment. On the other hand, ANAs (only IgG type measured) were sometimes detectable even 1-3 years after infliximab withdrawal. Neither infliximab nor etanercept induced other lupus-related reactivities such as anti-ENA or anti-histone antibodies and no clinically relevant lupus-like symptoms were observed. Similarly, infliximab but not etanercept selectively increased IgM but not IgG aCL titres.

The study confirms that the prominent ANA and anti-dsDNA response is not associated with other serologic or clinical signs of lupus. Thus, labs should be aware of the possibility of “false” positive ANA and anti-dsDNA response in patients on such treatment regimes. As the anti-dsDNA response is almost exclusively of the IgM isotype, results from assays such as RIA or other ‘mixed conjugate’ systems will particularly be affected.

August 08/05:

Fluctuation of ANA

Systemic lupus erythematosus (SLE) is the disease with probably the greatest variety and frequency of autoantibodies. According to the 1997 revised ACR criteria, antibodies to native DNA, anti-Sm, anti-phospholipid antibodies and antinuclear antibodies are relevant for the classification of SLE and therefore also play a major role in diagnosis. The serum concentration of anti-dsDNA antibodies may have a positive correlation with lupus nephritis activity. Accordingly, rheumatologists frequently measure anti-dsDNA antibody levels at different stages of the disease. In contrast, antinuclear antibodies (such as anti-U1-RNP, anti-Sm, anti-Ro and anti-La) are not routinely measured as part of disease follow-up, as no clinical association with titre variation is assumed. The authors of the following article studied the frequency of fluctuation of ANA and anti-dsDNA antibodies by analysing retrospectively the results of serial determinations in a cohort of SLE patients.

> Carvalho Faria A, Spat Albino Barcellos K, Coelho Andrade LE (2005)
> Longitudinal Fluctuation of Antibodies to Extractable Nuclear Antigens in Systemic Lupus Erythematosus
> *J Rheumatol 32, 1267-1272*

130 patients who fulfilled the ARA criteria for SLE with at least 5-yearly ANA and dsDNA were retrospectively measured for anti-dsDNA with CLIFT and for ANA, namely of anti-U1-RNP, anti-Sm, anti-Ro and anti-La by Ouchterlony double immunodiffusion.

ANAs	antytime pos	initial visit pos	pos. sero-conversion	neg. sero-conversion	always present
Anti-dsDNA	42 (32.2%)	28	14	24	4
Anti-U1-RNP	47 (36%)	37	10	19	18
Anti-Sm	30 (23%)	22	8	17	5
Anti-Ro/SS-A	61 (46.9%)	52	9	20	32
Anti-La/SS-B	9 (6.9%)	4	5	3	1

It was shown that the ANAs measured fluctuate over time in patients with SLE. It should be emphasized that the observed rates of longitudinal fluctuation of ANAs may represent a rather conservative estimate since at least 2 divergent test results were required for seroconversion definition. Moreover, some patients had only a 5-year follow-up period precluding detection of possible later seroconversion.

Anti-dsDNA and anti-Sm antibodies had the highest seroconversion rates among all antibodies. Anti-Ro/SS-A and U1-RNP antibodies presented a more stable data pattern. More than 60% of patients with positive tests at diagnosis for one of these 2 autoantibodies were still positive over 5 to 10 years.

No attempt to address possible associations of ANA fluctuation with disease activity and/or treatment was made due to the retrospective nature of the study. The results of this study show that ANA status frequently fluctuates in SLE patients over time. It would be very interesting to assess the correlation between these fluctuations and disease activity and/or therapy.

July 07/05:

ANCA-associated vasculitis: Risk factors for relapse

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are associated with autoantibodies against neutrophilic enzymes. In Wegener's granulomatosis (WG) ANCA are mostly directed against proteinase 3 (PR3), whereas a large number of patients with microscopic polyangiitis, idiopathic necrotizing crescentic glomerulonephritis and Churg-Strauss syndrome have antibodies against myeloperoxidase (MPO).

Current treatment based on the use of cyclophosphamide and corticosteroids has changed ANCA-associated vasculitides from highly fatal into more chronic, relapsing diseases. Long-term follow-up of patients with WG showed a relapse rate of 50% or more within 5 years after diagnosis, and active disease during relapses and treatment were important causes of mortality beyond the first year.
Therefore, a major challenge in current long-term treatment is the identification of patients at increased risk for relapse and the prevention of these relapses with minimal treatment-related toxicity. In the following article, recent studies that discuss the risk factors for relapse of disease and the potential preventive strategies are reviewed.

> Sanders JSF, Stassen PM, van Rossum AP, Kallenberg CGM, Stegeman CA (2005)
> Risk factors for relapse in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis: Tools for treatment decisions?
> *Clin Exp Rheumatol 22 (Suppl 36), S94-S101*

Several factors, such as ANCA-status during follow-up, levels of T cell activation, genetic background, and infectious and other exogenous factors have been associated with the occurrence of relapses in AAV. Compared to MPO-ANCA positive patients, patients with PR3-ANCA associated vasculitis run a significantly increased risk of experiencing relapses (3-fold higher risk for relapse within 5 years following diagnosis). The lower absolute risk for relapse in MPO-ANCA-associated vasculitis makes it probable that prolonged maintenance treatment in this group will not be worthwhile.

Patients who remain or again become PR3-ANCA positive during induction of remission have an increased relapse risk, which could indicate that these patients may benefit from prolonged immunosuppressive maintenance therapy. However, the toxicity of long-term immunosuppression could outweigh the benefit of a potential reduction in relapses. In an ongoing study the authors are currently evaluating whether long-term treatment in patients who remain PR3-ANCA positive after the induction of remission indeed reduces the occurrence of relapse.

Several genetic factors have been identified as risk factors associated with relapse. So far the applicability of these factors in individual treatment strategies appears limited and data on treatment adaptations based on these factors are absent. Exogenous factors, particularly chronic nasal carriage of *Staphylococcus aureus*, have been identified as risk factors for relapses in WG. Whether or not caused by an effect on *S.aureus*, trimethoprimsulfamethoxazole has been proven effective in preventing relapses in WG and maintenance therapy in patients with WG should be considered.

In this review, many potential relapse-predictors, (of which PR3 (ELISA) appears to be the most promising) are discussed. Further studies to verify whether the benefits of treatment based on this factor outweigh the potential side-effects of long-term immunosuppression are needed.

June 06/05:

Autoantibodies in Sjögren's syndrome

The typical markers in Sjögren's syndrome (SS) are antibodies to the Ro ribonucleoproteín (RNP) complex, namely Ro/SS-A 60 kD, Ro/SS-A 52 kD and La/SS-B. There is evidence that the proteins La and Ro 60 bind directly to the RNA molecule. The fact that Ro52 does not have a specific RNA binding sequence like Ro 60 and La has led to controversy about whether Ro52 is a true Ro RNP protein. This controversy goes along with the discussion whether Ro52 has clinical relevance for Sjögren's syndrome or not and, as a consequence, whether an assay for the detection of anti-Ro antibodies should contain both, Ro60 and Ro52 or if Ro60 alone is the only "real" Ro antigen. Several publications of the last 20 years reported a high clinical relevance of anti-Ro52 but on the other side, many immunologists doubt the usefulness of this marker. In the following publication a Norwegian group performed a detailed characterization of the serological pattern against the Ro and La autoantigens in terms of antigen specificity:

> Garberg H, Jonsson R, Brokstad KA (2005)
> The serological pattern of autoantibodies to the Ro52, Ro60, and La48 autoantigens in primary Sjögren's syndrome patients and healthy controls
> *Scand J Rheumatol 34, 49-55*

Sera from 100 patients fulfilling the European classification criteria for primary SS (1993) and 100 matched healthy controls were examined in this study. The SS group was further divided into patients who also fulfilled the 2002 criteria, and those who would not be regarded as having primary SS by the new criteria.

Using ELISA, the group of SS patients selected by the 1993 criteria showed a frequency of 62%, 24%, and 45% of positive serology against Ro52, Ro60, and La48, respectively. Applying the 2002 criteria, 66 subjects fulfilled the new criteria, and these frequencies increased to 71%, 33%, and 56% for Ro52, Ro60, and La48, respectively. Very few patients had antibodies towards La48 or Ro60 alone, while 20 % of patients had only Ro52 antibodies and would have been missed in a lab, which only looks for Ro60. In the apparently healthy controls, antibodies against Ro and La were also detected, with the highest frequency of 15% against La; 12% had anti-Ro52 and 4% anti-Ro60. Titres were significantly higher in the positive sera from SS patients than in these controls. The IgG isotype (which is often the only one detected in routine) was found in 8%, 2%, and 9% for Ro52, Ro60, and La48, respectively. These figures correspond to the literature.

An interesting finding in this study is that 4% of the SS patients and 12% of the controls had only anti-La. In the literature, it is reported that anti-La autoantibodies are invariably accompanied by anti-Ro, reflecting the physical association of the antigens in the ribonucleoprotein particle. The reason for the results obtained in the present study is not known.

This study gives clear data about antibody prevalences in Sjögren's syndrome – facts that are often missed in the discussion if anti-Ro52 is a relevant clinical marker or not. However, further studies with carefully chosen disease controls would give also interesting data on the clinical specificity of these markers.

May 05/05:

Anti-CCP Antibodies as Predictive Markers

On the 25th of April, the CCP-Symposium of Pharmacia Diagnostics was held. Main presentations were about clinical picture, diagnosis, and therapy of rheumatoid arthritis. Several short presentations showed the good clinical value of EliA CCP. In the discussions, the question arose if patients with positive anti-CCP results but without rheumatoid arthritis go on to develop rheumatoid arthritis in the future. The ability to predict the development of RA in patients with very early inflammatory arthritis is important if therapy is to be targeted at such patients. The objective of the following publication was the predictive value of anti-CCP antibodies:

> Raza K, Breese M, Nightingale P et al (2005)
> Predictive value of antibodies to cyclic citrullinated peptide in patients with very early I nflammatory arthritis
> *J Rheumatol 32, 231-238*

Antibodies to CCP and rheumatoid factor (RF) were measured in 221 patients. 124 patients with established inflammatory and non-inflammatory diseases were assessed in a cross-sectional study. Anti-CCP was positive in 3 of 52 patients with non-RA inflammatory disease, and was not detected in patients with non-inflammatory disease. The specificity and sensitivity of the presence of anti-CCP antibodies for a diagnosis of RA were 96% and 57%, respectively. Additionally 97 patients with very early inflammatory arthritis (synovitis of at least one joint an d a symptom duration of $\leq$ 3 months) were assessed and followed up. 24 (25%) of these patients were classified as having RA at some point during follow-up and 72 (75%) were not. Of those 24 fulfilling the ACR criteria for RA, 19 had persistent disease and 5 had disease that resolved during follow-up.

This is the first study that has assessed the utility of anti-CCP in patients with very early inflammatory arthritis. According to the authors, it is possible that treatment may have had an effect on the development of sufficient ACR criteria necessary to classify patients as having RA. Thus, for example, 17 of the 23 patients with non-RA persistent arthritis had been treated with a second-line anti-rheumatic drug or oral prednisolone. In theory, some of these patients may have developed criteria to allow classification as RA had these medications not been commenced.

The authors found that seropositivity for a combination of both RF and anti-CCP was associated with a specificity and PPV of 100% for the diagnosis of RA. However, 21% of patients fulfilling classification criteria for RA had disease that resolved on follow-up. The utility of the 1987 ACR criteria in early disease has been questioned as their PPV for disease persistence at 3 years is only 82% by tree format and 85% by list format.

The combination of RF and anti-CCP was the strongest independent predictor of the development of persistent RA. RF alone had a relatively high specificity in the population used in this study. However, combining RF with anti-CCP afforded some additional specificity. “This may be important if the presence of these autoantibodies is to influence treatment decisions in very early synovitis, where minimizing exposure of patients who are not going to develop RA to potentially toxic therapy is desirable.”

April 04/05:

Screening for Celiac Disease

Celiac disease is an immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals. As the high sensitivity and specificity of the marker anti-tissue transglutaminase (anti-tTG) becomes increasingly well recognized, diagnostic routine is undergoing changes towards greater emphasis on antibody testing. In this context, the Celiac Disease Guideline Committee of the NASPGHAN (North American Society for Pediatric Gastroentereology, Hepatology and Nutrition) has formulated a clinical practice guideline for the diagnosis and treatment of pediatric celiac disease based on an integration of a systematic review of the medical literature combined with expert opinion. The guidelines were published in the following:

> Hill ID, Dirks MH, Liptak GS, Colletti RB, et al. (2005)
> Guidelines for the diagnosis and treatment of celiac disease in children: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
> *J Pediatr Gastroenterol Nutr 40, 1-19*

It is recommended that children and adolescents with symptoms of celiac disease or an increased risk for celiac disease have a blood test for antibodies to tissue transglutaminase. Anti-tTG ELISA is recommended, because EMA is observer-dependent and more costly. Those with an elevated tTG should be referred to a pediatric gastroenterologist for an intestinal biopsy and those with the characteristics of celiac disease on intestinal histopathology should be treated with a strict gluten-free diet. This recommendation by the NASPGHAN will certainly have an impact on the upcoming ESPGHAN guidelines and thus will most likely become a standard worldwide.

This leads to the question, who is at increased risk for celiac disease. Several studies have shown that celiac disease is associated with autoimmune disorders including type I diabetes, autoimmune thyroid disease, Sjögren's syndrome, autoimmune liver disease and Addison's disease. In the following two articles, the authors determined the prevalence of celiac disease in osteoporosis and Graves' disease:

> Stenson WF, Newberry R, Lorenz R, Baldus C, Civitelli R (2005)
> Increased prevalence of celiac disease and need for routine screening among patients with osteoporosis
> *Ach Intern Med 165, 393-399*

> Ch'ng CL, Biswas M, Benton A, Jones MK, Kingham JGC (2005)
> Prospective screening for coeliac disease in patients with Graves' hyperthyroidism using anti-gliadin and tissue transglutaminase antibodies
> *Clin Endocrinol 62, 303-306*

Stenson et al. found that the prevalence of celiac disease among osteoporotic individuals is much higher than that among non-osteoporotic individuals (3.4 % vs 0.2 %). Treatment of the patients with celiac disease with a gluten-free diet resulted in marked improvement in osteoporosis indicators. The authors conclude that the prevalence of celiac disease in osteoporosis is high enough to justify a recommendation for serologic screening of all patients with osteoporosis for celiac disease. Given the high prevalence (3.5 – 9.3 %) of osteoporosis, this study suggests the possibility of improving the quality of life for a significant number of patients.
Similarly, Ch'ng et al. found that the prevalence of celiac disease in patients with Graves' disease was 4.5 % as compared with 0.9 % in matched healthy controls. The authors conclude that routine screening for CD should be considered.

With the changes in diagnostic routine, screening patients with a high risk of celiac disease is increasingly considered. The importance of choosing a highly specific assay for use in a screening context should not be underestimated.

March 03/05:

Review on anti-CCP

EliA CCP was launched at the Autoimmunity Congress in Budapest, November 2004. A number of evaluations carried out with EliA CCP and presented at the congress confirmed the value of the marker in general and the high quality level of EliA CCP in particular. Since its launch, EliA CCP has been implemented by several customers worldwide into their routine testing, and increasing interest in the test has been expressed by other laboratories and clinicians. Several of the questions frequently asked relateto the prognostic value of CCP antibodies. In this respect, the following article by the CCP group of Professor van Venrooij on this topic gives an excellent overview on the current status of discussion.

> Zendman AJW, Vossenaar ER, Van Venrooij WJ (2004)
> Autoantibodies to Citrullinated (Poly)Peptides: A Key Diagnostic and Prognostic Marker for Rheumatoid Arthritis
> *Autoimmunity 37, 295-299*

After reviewing the sensitivity and specificity data of rheumatoid factor and filaggrin-associated antibodies, the authors describe the diagnostic use of anti-CCP antibodies. In table 1 the sensitivity and specificity of CCP2 vs. IgM-rheumatoid factor are compared. In table III features of predictive and prognostic CCP studies are listed, which show clearly the predictive and prognostic use of anti-CCP antibodies.

In addition to this article, we have attached a review by Dr. Gaubitz, that he wrote as information for customers for the German Market Company and which he handly allowed us to distribute internationally as well.

February 02/05:

Diagnostic Accuracy of SLE

Connective tissue diseases are systemic diseases and occur with a very widespread clinical picture. The early manifestations of diseases such as systemic lupus erythematosus or systemic sclerosis are often of a general nature such as low fever, general weakness, fatigue etc. Thus, especially for general practitioners who do not see these diseases every day, it may be very difficult to establish the diagnosis in an early stage of the disease. Positive ANA results can lead to overdiagnosis, with the consequence of inappropriate treatment with potentially dangerous medications. Conversely, underdiagnosis can lead to a delay in appropriate therapy, culminating in irreversible complications such as renal failure or pulmonary fibrosis. In the following study from the University of Florida, the authors evaluated community physicians' accuracy in diagnosing autoimmune diseases and the consequences of misdiagnosis:

> Narain S, Richards HB, Satoh M et al. (2004)
> Diagnostic Accuracy for Lupus and Other Systemic Autoimmune Diseases in the Community Setting
> *Arch Intern Med 164, 2435-2441*

The authors reviewed 476 sera seen in the course of one year in the University of Florida Autoimmune Disease Center, Gainesville. The referring physician was asked to complete a prescreening questionnaire indicating the reasons for referral and a working diagnosis.

Most patients were referred with the diagnosis of SLE (56%). 49% of the referring diagnoses matched the final diagnoses, and 129 patients received an incorrect diagnosis of SLE. The authors calculated the sensitivity, specificity, accuracy, and positive and negative predictive values for the referring physicians' diagnoses. Diagnostic sensitivity was high for SLE (88%). High specificity was seen for all diagnoses except SLE (52%).
Many patients with a positive ANA test are incorrectly given a diagnosis of SLE and often treated with toxic medications. The authors conclude that increased awareness of the clinical presentation of these diseases may help increase diagnostic accuracy. There also may be a role for diagnostic pathways or algorithms to aid in determining which patient should be referred to a specialist.

Additionally, the results of this study show the importance of detailed ANA testing with single parameters. ANA positivity, as found by immunofluorescence, should never be a stand-alone result but must be embedded in the whole serodiagnostic and clinical picture.

January 01/05:

ANCA and anti-GBM

Anti-Neutrophil Cytoplasmic Antibodies (ANCA) which bind to either myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA), are associated with small vessel vasculitis such as microscopic polyangiitis and Wegener's granulomatosis. Anti-glomerular basement membrane antibodies (anti-GBM) are markers of Goodpasture's disease and the so-called anti-GBM disease, with the typical involvement of lung and kidney.

A number of patients have both sets of autoantibodies simultaneously coexisting. The frequency of patients with anti-GBM antibodies having ANCA has been estimated as 30-38%, and 7.5-14% of those with ANCA have anti-GBM. The clinical outcome of these patients remains poorly defined. The authors of the following study have determined the prevalence of patients with both types of autoantibody in a large series and describe their clinical outcome:

> Levy JB, Hammad T, Coulthart A, Dougan T, Pusey CD (2004)
> Clinical features and outcome of patients with both ANCA and anti-GBM antibodies.
> *Kidney Int 66, 1535-1540*

The authors reviewed all sera tested between 1990 and 2000 in the laboratory of the Hammersmith Hospital in London. During this time 20,392 sera were initially tested for ANCA, and 4,808 sera were tested for anti-GBM antibodies.

5% of all ANCA-positive serum samples were also positive for anti-GBM and 32% of all anti-GBM positive samples had detectable ANCA. Of 27 patients with both antibodies, 82% had anti-MPO specific p-ANCA. Patient and renal survival rates were 52% and 26%, respectively, at one year. 68% of patients were dialysis-dependent at presentation, and none of these recovered renal function.

The authors concluded that serologic evidence of double positivity for both ANCA and anti-GBM is common in patients with either antibody. These patients have a poor prognosis when presenting with severe disease and initially behave more like anti-GBM disease than vasculitis. Recovery from severe renal failure is rare and, in this study, did not occur.