Incomplete Lupus Erythematosus
by
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Definition
Incomplete Lupus Erythematosus (ILE) refers to a condition where patients present with signs of systemic autoimmunity and clinical symptoms compatible with Systemic Lupus Erythematosus (SLE), but presently do not fulfil four of the ACR criteria required for classification of SLE (1).

Background
The introduction and subsequent updating of classification criteria has been a major step forward in studying the epidemiology, prognosis and underlying immune disturbances in SLE. The statistical procedures underlying classification aim for the lowest amount of heterogeneity in cohorts and thus excluded patients with fewer than four typical or other symptoms suggestive of SLE. This stringent classification process has introduced a clinical dilemma that has received too little recognition. Currently, the fulfilment of ACR criteria is often regarded and recommended as the absolute requirement for the diagnosis of SLE in clinical practice, even though the proposed model was only meant to facilitate formal communication in scientific papers. The authors involved in the classification process have never proposed their use as diagnostic criteria(1). It should be remembered that during the classification process a considerable amount of clinically useful information was excluded to achieve the model that best discriminated between SLE patients and other disease types (2). Specifically, this may lead to situations where patients with SLE are not given the diagnosis and are even in danger of not receiving appropriate treatment because of not fulfilling four ACR criteria. In addition, such patients are systematically excluded from therapeutic trials in SLE, which reducing the impact of these important studies (Costenbader, 2002). Most rheumatologists will readily acknowledge that SLE is a much more diverse clinical syndrome, than suggested by the narrowly defined ACR criteria set. This is also reflected in the manner by which various scoring systems for disease activity such as SLEDAI, BILAG and ECLAM were developed; they incorporate a wide range of disease manifestations (e.g. vasculitis, fever) not included in the ACR criteria, because these manifestations are considered important in individual patient management. Finding isolated immune complex mediated glomerulonephritis in an ANA positive patient will carry a different weight during patient evaluation than finding isolated UV hypersensitivity and discoid lesions in that ANA positive patient. The importance of severe manifestations thus often overrules the amount of classification criteria fulfilled in the diagnostic process and subsequent management (Gilboe, 1999); this seems of particular relevance for childhood SLE, where presentation is diverse and often severe (Bader-meunier, J ped2006).

Figure 1 details the frequency of a variety of non-ACR based findings for skin, vascular and serologic manifestations of SLE in relation to ACR criteria from a cohort study of European patients with severe SLE (Nossent 2007).

To compensate for this lack of flexibility of the ACR classification, several authors have proposed weighting of the various ACR criteria (5;6). In this process, different point scores are given to a range of skin, renal, CNS, joint and serological manifestations. Applying the latest Boston weighted score allowed SLE diagnosis in patients with e.g. leukocytopenia and a positive ANA and increased total SLE cohort size by 20 % (Costenbader 2002). Another problem with the current use of the ACR criteria set is its failure to take into account that several disease manifestation in SLE are interdependent as best exemplified by the strong correlation between anti-dsDNA Ab and positive ANA (7). This leads to a situation where in reality only three classification criteria are fulfilled (as the anti-dsDNA antibodies also cause the positive ANA) and
patients nonetheless are classifiable as SLE. The resulting skewing of clinical and scientific data has thus far received little attention.

All the above serves in our opinion to strengthen the concept that as long as ACR criteria remain a gold standard in clinical practice, ILE as defined above is not only an appropriate term for patients presenting with less than four ACR criteria and/or other lupus related manifestations, but constitutes a genuine clinical entity. Although ILE is currently also being named sub-clinical lupus, variant lupus, latent lupus or non-classic lupus, ILE would be the preferred acronym (8-13). Our current assumption that ILE patients are at risk of developing a more severe disease entity in the future provides a clinical challenge. Recognition of ILE is directly important in patient management, but increased attention on ILE may lead to a better understanding of the mechanisms by which the immune disturbances occurring in ILE patients do not translate into a severe clinical phenotype. Scientific studies on early recognition of ILE and therapeutic measures to prevent the development of more severe disease may be one of the most fruitful measures in our efforts to relieve the burden of disease for SLE patients. This can provide important ideas for the whole field of systemic autoimmunity.

**ILE versus undifferentiated connective tissue disease (UCTD)**

SLE is nowadays a disease that develops gradually over time and only a minority of patients present with acute multi-system disease, which can promptly be classified according to the presence of four or more ACR criteria. In the LUMINA study cohort 15% of patients presented in this manner and the average time needed to accrue four ACR criteria was more than three years for patients with only one ACR criterion at first presentation and 2.5 and one year respectively for patients presenting with two or three validated ACR criteria (15). One can thus say that most SLE patients have been going through a period where there disease was ILE, which ultimately became progressive. The longest lagtime between ILE onset and fulfillment of the scientific diagnosis of SLE was 328 months, indicating that even very late disease progression may occur in ILE (15). Similarly, in studies based on SLE patients for whom pre diagnosis serum was available from a US military serum repository, 80% of patients had a gradual accrual of serological and clinical disease criteria (Arbuckle M, 2001, Heinlen LD 2007). While these cohort studies excluded patients with non-progressive ILE, they clearly show that in most SLE patients a prior window of opportunity exists, where early ILE diagnosis and intervention can take place in order to prevent development of more severe disease.

After ANA testing became more widely available between 1980 and 1990, the term undifferentiated connective tissue diseases (UCTD) was introduced to designate an increasing numbers of patients were seen with sporadic manifestations compatible with systemic autoimmune disease and a positive ANA test. However, despite proposed criteria for its classification, UCTD is not an established entity (Mosca 2007) with the name reserved for those patients with features strongly suggestive of an autoimmune rheumatic disease, but not readily classified as a specific CTD (18). Published UCTD series contain variable numbers of ILE patients in addition to patients with not yet fully recognised RA or Scleroderma (19;20). As UCTD and ILE share a considerable number of characteristics, the distinction between the two conditions is not very clear suggesting to some authors that they should be considered one and the same condition (Panush,1993, Venables 1998). The question will not be solved until our current lack of data on the subject is addressed. For all practical purposes (Doria A , 2005) one might consider ILE to be a subset of UCTD, where presenting features already indicate the potential for SLE development (Figure 2).

**Epidemiology**

There has been only one report on the epidemiologic characteristics of ILE. A long-term disease registry in the Danish county of Funen with a population of nearly 400,000 has with the use of capture/recapture techniques estimated the annual ILE incidence to be 0.4/100.000 and an ILE
point prevalence of 7/100.000 in 2003. It should be noted that these are data from an area with one of the lowest reported SLE incidence (1.0/100.00) and prevalence (29/100.000) rates world wide (Laustrup, Voss). Given the additional selection bias towards definite SLE, these rates thus represent minimum estimates. Based on compiled longterm observational data from Southern Sweden, an annual ILE incidence of nearly 2/100.000 can be inferred (12;21). Other cross sectional studies indicate that ILE is not uncommon and occurs with similar frequency in Caucasian as in other ethnic populations (9;10;22) (Haider, 2006- Wanst 2006). Epidemiological data on ILE from areas with a high incidence rate of SLE are much needed to address the question to what extent ILE can be considered a subset of SLE in various populations.

Clinical presentation
At present, seven studies have been reporting on dedicated ILE cohorts in several regions. Despite slightly differing inclusion criteria, the demographics of patients included in these studies show that age and gender distribution are largely similar to patient characteristics in SLE cohorts (Table 1). The frequencies of the main clinical in these studies are depicted in Figure 3. Skin and joint affection and cytopenias are the most frequent manifestations. With the exception of the Swedish study, there is a very low frequency of renal involvement with no cases of end-stage renal failure reported. All studies report a virtual absence of neurological ACR criteria, which is not surprising given their low sensitivity in SLE classification. Serological findings (Figure 4) show that the presence of ANA is most frequently an isolated finding and when subspecificities are detected, the rate of anti-Ro/La antibodies exceeds the rate for anti-Sm or anti-dsDNA antibodies.

Disease course in ILE
Clinical phenotype The rate of progression to an ACR criteria based definition of SLE in dedicated ILE studies is summarised in Table 4. The highest progression rates were described in studies with the longest follow up, consistent with the finding that ILE may continue evolve to classical SLE after prolonged periods. Few clinical features consistently predict progression to SLE. The rate of SLE progression was independent of gender and ethnicity did not differ between in the US military study, while presentation with malar rash was related with more rapid progression in two study (heinler 2007) (stahl). The presence of anti-dsDNA and antiphospholipid antibodies as well as low complement levels (stahil, villa) were found to be the most reliable serological predictors of progression to SLE. Thus, while prolonged observation of ILE patients is indicated for many years, the risk for SLE progression is highest within the first four years and may be predicted by the presence of antibody clusres (To and Petri, 2005) (Jurenczak 2009). Several UCTD cohort studies have also reported rates of progression to SLE. In these more broadly defined cohorts, the percentage of patients with presumed ILE, that subsequently progressed to SLE varied strongly from 12-95 % (Cavazanna 2001, Mosca 2002, Bodolay 2003).

Disease activity Two studies have reported measures of disease activity in ILE cohorts. The European multicenter study with the largest cohort (n=122) followed patients over 3 years (11). The development of disease activity over time (SLEDAI and ECLAM scores) (Table 3) shows that ILE patients had persistent low disease activity over the three-year period in contrast to patients progressing to SLE; in these patients disease activity scores increased sharply, indicating that this progression was characterised by multisystem activity rather than the gradual accrual of one more ACR criterion. However, the validity of these scoring systems in ILE patients has not been assessed and given their organ-based approach they may well lead to underestimates of disease activity in ILE.

This can be illustrated in a more detailed analysis of the changes in specific disease manifestations. At group levels, there is relatively little change in the frequency of specific organ manifestations over three years of follow-up (Figure 5A), with the exception of an increase in malar rash and non-hemoytic anemia prevalence. More detailed information on the type and
number of ILE patients experiencing disease activity can be gathered from Figure 5B, that captures dynamics at the individual level. Here the annual number of ILE patients experiencing specific clinical features is given as a function of that manifestation in the previous year by the percentage of patients with increasing, stable or decreasing symptoms. Such data provide better insight in the active process of disease activity changes in individual patients than the small changes seen in overall SLEDAI scores (Table 4) and percentage of patients with the relevant manifestation (Fig 5A). As an example, the prevalence of arthritis changes from 15% to 19% and to 13%, but there were considerable larger variations in the number of patients remitting and experiencing new arthritic flares. The frequency of renal involvement showed a different pattern with no new cases emerging during observation. The most frequently observed laboratory finding was leucocytopenia, which despite an overall reduction in prevalence from 36 – 20% during follow-up at the group levels, showed nearly similar proportions of new and remitting cases. Similar findings for anaemia of chronic disease, where overall prevalence rose from 10% to 11% and 16%, despite a large proportion of patients with ACD remitting during observation. These data all confirm the position, that ILE is not a continuous grumbling disease state, but in line with SLE has a fluctuating disease course.

**Damage development** Few data are available to determine whether the fluctuating disease activity in ILE patients will lead to permanent organ damage. In the Swedish cohort the mean SLICC damage index did not increased significantly from 0.1 to 0.2 during long term follow-up of ten years and only 2/12 (16%) of non progressing ILE patients developed organ damage (12), indicating that the previously mentioned persistent but low disease seems relatively benign. In contrast 10/16 (63%) of patients progressing to SLE developed organ damage with a mean score of 1.5 (Stahl 2004).

**Other outcomes** While outcome measures such as mortality, cardiovascular morbidity (given the relation between chronic inflammation and plaque formation) as well as quality of life are of clinical interest, these have not been reported yet for ILE patients. Data extractions from the referred ILE cohorts’ studies describe one case fatality in non-progressing ILE patients. An important aspect of outcome studies is the potential influence of therapeutic interventions. Despite a lack of data, drug treatment is evidently not a rare occurrence as considerable numbers of patients are prescribed NSAID, antimalarials and oral corticosteroid therapy (Table 7). In the ESCISIT study 38% of patients were at inclusion already on treatment with prednisolone (none with doses higher than 10 mg/day). This figure changed to 43% and 27% in year 2 and year 3 respectively. For antimalarials these figures were 17% and 32% respectively, while Azathioprine was prescribed in only 2%, 3, 5% and 4.5% of cases respectively. The influence (if any) of these treatment regimens on disease expression and the progression to SLE has not been studied in a controlled fashion. A retrospective analysis of the US military SLE study nonetheless showed that both OH chloroquine and corticosteroic treatment significantly increased the time from first onset of clinical symptoms to SLE progression, while OH chloroquine treatment also reduced the subsequent number of autoantibody specificities (James 2007). No such effect was seen for NSAID treatment. These important preliminary findings provide limited support for the early use of immunosuppressive therapies in ILE, although more detailed data on the indication and timing of therapies are clearly needed.

**Pathogenesis: Is ILE a subset of SLE?**

Based on the considerable clinical and serological similarities, it seems reasonable to presume that ILE patients share at least a part of the aetiopathogenesis with SLE. Based on the observations, that autoantibodies can be detected in the sera of SLE patients long before they accumulate enough ACR criteria for classification (Arbuckle 2003) a hypothesis that can be formulated that while ILE patients produce the same spectrum of auto-antibodies as SLE patients, these antibodies fail to attain the same level of pathogeneticity. In general, IgG type autoantibodies are
presumed to be more pathogenic (i.e. nefritogenic) than IgM type antibodies in SLE due to affinity maturation (Rekvig/Nossent 2003). Thus the idea can be put forward that while ILE patients produce the same auto-antibodies as SLE patients, they “fail” to make the switch from IgM isotype to IgG isotype autoantibody production. Comparing the autoantibody isotypes between SLE, ILE and first-degree relatives of SLE patients, serum of ILE and SLE patients contained high levels of IgG autoantibodies to 50 autoantigens and IgM autoantibodies to 12 autoantigens. The IgG: IgM autoantibody ratio however showed a stepwise increase in the groups with growing disease burden, indicating that IgM autoreactivity predominates in ILE and that this may represent an early stage prior to IgG switching or developing SLE (51). However an alternative explanation is that ILE patients form a stable group, which by unknown regulatory systems the affinity maturation process and the forming of IgG autoantibodies is halted. This could form an explanation for the finding that the non progressing ILE patients represents a subgroup with a good prognosis. While our knowledge is far from complete, important lessons can thus be learned by closely studying the immunological process in ILE patients.

Aethiopathogenesis: similarities between SLE and ISLE

CRP, SAP and IgM compete with each other for binding to apoptotic cells suggesting they share similar binding sites (CE Hack, 2006). Knockout of IgM (Boes et al., 2000; Ehrenstein et al., 2000) or acute phase reactants (Bickerstaff etal., 1999) leads to lupus-like diseases with impaired handling of apoptotic cells.

This data suggest that in ILE patients the dominating IgM immune response may be related to a better and protective CRP response than in SLE. Several relevant mechanisms may be operative in hindering progression to SLE, that will need further study:

C-reactive protein (CRP) is an acute-phase protein that in lupus prone mice exerts therapeutic activity by protecting against glomerulonephritis (Du Clos Clin Imm 2005). The mechanism by which CRP suppresses immune complex mediated disease may involve its binding and removal of autoantigens, that are released during apoptosis as well as the induction of suppressive macrophages through FcRI activation.

While median CRP levels in RA are in the range of 20-40 mg/liter (32), in SLE patients with an exacerbation levels are seldom above 15 mg/liter (33). However a marked CRP response can be found in SLE patients with serositis, synovitis and bacterial infections (34)(35), where CRP levels may exceed 50 mg/liter. It is unclear whether this indicates a general abnormality of the CRP response in all SLE patients or whether this points to the presence of subsets of SLE patients with a specific alteration in the CRP response. This would require SLE patients with a diminished CRP response during nephritis to show the same response when developing by example an serositis. In our studies of the acute phase reaction this pattern was not observed, but a diminished CRP production was associated with increased production of ferritin during development of nephritis (36). Thus the reduced CRP response seems to represent an isolated defect in the APR in SLE as supported by increases in other acute phase proteins α1-acid glycoprotein and fibrogen (37) (38,39). The induction of the acute phase proteins is regulated by a concerted action of cytokines in which TNF as well IL-6 play a dominant role (40) Overall a correlation between IL-6 and CRP levels is claimed, but a deficiency in IL-6 production could not demonstrated by using whole blood cell cultures, but in patients treated with prednisone a diminished production could be calculated (41).

That the acute phase reaction may be very important in the aethiopathogenesis of the disease or in the autoantibody production is illustrated by the following observations:

- CRP gene polymorphisms, that contribute to low basal CRP levels is associated with the production of antinuclear antibodies and lupus nephritis (42,43).
- studies on mouse models of SLE showed that application of CRP might have a beneficial effect (44).
- In humans more direct evidence is obtained by the fact that treatment of RA patients with anti-TNF, by which a blunted CRP response can be proposed to be induced, in a significant amount of patients auto-antibodies are demonstrated (45,46).

CRP, among other molecules is needed for an efficient clearance of apoptotic cells. These observations sustained the hypothesis that by a less than normal CRP production a defective clearance of cell debris or apoptotic cell material can be the cause of an increased immunogenicity of cell fragments. In other words the alternative way for the clearance of this cell debris is by the production of specific antibodies directed to fragments of the cell debris to facilitate the clearance, however in this way leading to the formation of auto-antibodies. In first instance the antibodies will belong to the IgM Class, but it is to be expected that also later on IgG antibodies will be formed. In time these auto-antibodies will become more pathogenetic. Different kind of auto-antibodies can produced; antibodies against cell membranes, like erythrocyte, or granulocyte antibodies, or cell fragment, such as ANA, but also proteins; RNA, dsDNA, etc. In this way cytotoxic and antibodies forming immune complexes can be formed.

Next to CRP other acute phase reactants are important for the clearance of cell debris like the mannan binding protein or the complement system (47,48). Deficiencies in both systems are also correlated with the formation of auto-antibodies and the presence of symptoms related to SLE. That the above pathogenic pathway may be operative is further sustained by the observation of INF alpha administration to patients with melanoma which is followed by a decrease in CRP levels, in contrast to ferritin levels which increase (49). But recently in these patients an increase in auto-antibodies production is demonstrated (50).

That the same pathogenetic pathway in ILE may be operative as in SLE is sustained by the fact that they do not differ in the average age of disease onset, but most of all they were characterized by a comparable ferritin:CRP ratio (table 5) which is quite different compared with RA patients.

**Summary**

When a patient fulfils ACR classification for SLE, the case is considered classic and the diagnosis is readily accepted. Patients who fulfil less 2-3 ACR criteria or have other representative SLE manifestations have incomplete Lupus Erythematosus (ILE). ILE is a relatively common distinctive disease entity and usually presents with rash, Raynaud’s phenomenon, arthritis, leucocytopenia and thrombopenia together with antinuclear antibodies and one subspecificity. Longterm followup of ILE patients is required. Many patients will have a benign disease course with varying periods of disease activity, but with current management, 10-50 % will eventually progress to SLE, which may be retarded by OH-chloroquine treatment. While long-term disease remission is the ultimate goal of treatment for SLE patients, this is a relatively rare occurrence (ref). Treatment is often considered efficacious, when patients no longer have acute, life threatening complications despite the fact that many have intermittent or continuous low disease activity (Petri/Silverman/Font). Actually, such patients can be considered to have returned to a post-hoc state of ILE, with similar doubts about the long term prospects and optimal management as in the pre-hoc, non progressed ILE state. Closer study of ILE patients may provide important clues for our understanding of the pathophysiology and management of SLE.
References


(40) Swaak AJG inf limb perfusio


Figure 1 Frequency distribution of ACR criteria and other manifestations that are not included in the criteria set for skin, cardiovascular and serological manifestations of SLE
**Vascular**

- Arterial thrombosis
- Venous thrombosis
- Arterial hypertension
- Raynaud phenomena
- Avascular bone necrosis
- Two spontan. abortions

**Autoantibodies**

- ANA test
- Anti-DNA Ab (Farr)
- Anti-RNP Ab
- Anti-SSA Ab
- Anti-cardiolipin Ab (IgG)
- Lupus anticoagulant

**Skin**

- Periorbital eryhema
- Panniculitis
- Urticaria
- Purpura
- Discoid rash
- Butterfly rash

- Discoid rash
- Purpura
- Urticaria
- Periorbital eryhema

Figure 2 Graphical representation of the interrelationships between ILE, UCTD and defined CTS.
Table 1 Characteristics at presentation of patients included in clinical ILE studies.

<table>
<thead>
<tr>
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<th></th>
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<th></th>
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<tbody>
<tr>
<td>Geography</td>
<td>Denmark</td>
<td>United Arab Emirates</td>
<td>Sweden</td>
<td>Europe</td>
<td>Puerto</td>
<td>USA</td>
<td>Canada</td>
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<tr>
<td>Inclusion</td>
<td>≥1 ACR &lt;4</td>
<td>≥1 ACR &lt;4</td>
<td>≥1 ACR &lt;4</td>
<td>ANA + 1</td>
<td>≥1 ACR</td>
<td>≥2 ACR &lt;4</td>
<td>≥1 ACR ≤2 + one</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>organ &lt;4</td>
<td>ACR &lt;4</td>
<td>4</td>
<td>other symptom</td>
</tr>
<tr>
<td>No. included</td>
<td>37</td>
<td>12</td>
<td>28</td>
<td>122</td>
<td>87</td>
<td>38</td>
<td>22</td>
</tr>
<tr>
<td>Female (%)</td>
<td>100</td>
<td>80</td>
<td>93</td>
<td>99</td>
<td>94</td>
<td>84</td>
<td>90</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39</td>
<td>30</td>
<td>45</td>
<td>40</td>
<td>34</td>
<td>37</td>
<td>37.5</td>
</tr>
<tr>
<td>Symptom duration</td>
<td>-</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
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<td>38</td>
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</table>
Figure 3  Frequency of reported disease manifestations in ILE patients

- Malar rash
- Discoid lupus
- Photosensitivity
- Oropharyngeal ulcers
- Arthritis
- Serositis
- Glomerulonephritis
- CNS disorder
- Any hematologic disorder
- Anemia (any type)
- Haemolytic anemia
- Leucopenia
- Thrombocytopenia
- Constitutional
- Alopecia
- Raynaud

Frequency (%)
Figure 4 Frequency of reported auto-antibodies in ILE patients
Table 2  Progression to SLE in ILE cohorts (as defined by reaching four or more ACR criteria)

<table>
<thead>
<tr>
<th>Study</th>
<th>Laustrup (n=37)</th>
<th>Attia (n=15)</th>
<th>Stahl (n=28)</th>
<th>Swaak (n=122)</th>
<th>Villa (n=87)</th>
<th>Ganczarczyk (n=22)</th>
<th>Greer (n=63)</th>
<th>Combined 374</th>
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<tbody>
<tr>
<td>% reaching =&gt;4 ACR criteria</td>
<td>19 0</td>
<td>57 21</td>
<td>9 32</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Observation (yrs)</td>
<td>8 1,8</td>
<td>13,0 3,0</td>
<td>2,2 8,0</td>
<td>1,5</td>
<td></td>
<td></td>
<td></td>
<td>5,4</td>
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<tr>
<td>Months to ACR classification</td>
<td>98 .</td>
<td>64,0 14,0</td>
<td>52,0 60,0</td>
<td>18,0</td>
<td></td>
<td></td>
<td></td>
<td>43</td>
</tr>
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Table 3
Median disease activity scores (SD) at various time points in 122 patients initially diagnosed with ILE.

<table>
<thead>
<tr>
<th>Period</th>
<th>Stable ILE (n=97)</th>
<th>SLE Progression (n=25)</th>
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<tr>
<td></td>
<td>ECLAM</td>
<td>SLEDAI</td>
</tr>
<tr>
<td>0-12 months</td>
<td>2.1</td>
<td>2.6</td>
</tr>
<tr>
<td>13-24 months</td>
<td>2.1</td>
<td>2</td>
</tr>
<tr>
<td>25-36 months</td>
<td>1.7</td>
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Figure 5A  Frequency (% of whole cohort) of specified clinical findings in ILE cohort throughout three years of observation.
Figure 5B  Dymanics of changes in disease activity in ILE patients for specified clinical findings from first to second year and second to third year observation
<table>
<thead>
<tr>
<th></th>
<th>Swaak</th>
<th>Greer</th>
<th>Ganczarczyk</th>
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<tr>
<td>NSAID</td>
<td>NA</td>
<td>47</td>
<td>41</td>
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<tr>
<td>Antimalarials</td>
<td>17</td>
<td>29</td>
<td>NA</td>
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<tr>
<td>Corticosteroids</td>
<td>43</td>
<td>32</td>
<td>9</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>5</td>
<td>3</td>
<td>0</td>
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Table 5 Differences in demographic data between ILE, SLE and RA patients

<table>
<thead>
<tr>
<th></th>
<th>ISLE (Nos 20)</th>
<th>SLE (Nos 13)</th>
<th>RA (Nos 22)</th>
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<tr>
<td>Age at diagnosis (year)</td>
<td>31 ± 12</td>
<td>34± 13</td>
<td>45±13</td>
</tr>
<tr>
<td>Ferritin/CRP ratio* median (range)</td>
<td>11-19</td>
<td>13-15</td>
<td>8-20</td>
</tr>
</tbody>
</table>

*Data of those patients were selected during their disease course of at least 3 periods when CRP levels were > 10 mg/dl, infection excluded as well iron deficiency. Of the different ratio the average was calculated. All patients were for a longtime followed at our outpatient clinic for auto-immune diseases.