Early inflammatory clinics. Experience with early arthritis/back pain clinics

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ABSTRACT

There is a clear need to assess patients presenting with a new onset of inflammatory peripheral arthritis and/or back pain early. Indeed, the clinical presentation of rheumatoid arthritis (RA) is not always characteristic but its early diagnosis is crucial to prevent irreversible structural damage. Likewise low back pain is common in the general population but may be related to ankylosing spondylitis (AS) and other axial spondyloarthritis (SpA) in up to 5% of cases. Mounting evidence suggests that early intervention leads to improve outcome both in RA and SpA which has important socioeconomic implications. Early inflammatory clinics (EIC) should therefore be considered in every rheumatology department to facilitate the early assessment and diagnosis of these patients allowing for prompt and targeted therapeutic intervention. In addition the EICs allow for a better focused follow-up of these patients in appropriate secondary clinics. Since the sustained remission of inflammatory and autoimmune diseases such as RA is highly dependent on how early treatment is instigated and its efficacy regularly assessed, there is legitimacy for the EICs. Furthermore, there is a clear research interest in building early inception cohorts that allow for the characterization of the different disease phenotypes.

Introduction

Rheumatoid arthritis (RA) progresses to irreversible structural damage of the joints and must therefore be diagnosed and treated early, since the achievement of rapid suppression of inflammation to maximize disease control is critical (1). The prevalence of RA is estimated to be about 0.3 to 1% in most European populations. The annual incidence of early arthritis was recently assessed in the Spanish population and reported as 25 cases for 100,000 inhabitants, with an incidence of 8.3 RA cases for 100,000 (2). The clinical presentation of RA is not always characteristic at onset since various clinical phenotypes including mono and oligoarthritis can be seen. Moreover, the current classification criteria for RA were developed in established disease and therefore are not often fulfilled in the early stages of the disease. Autoantibodies such as rheumatoid factors and especially antibodies directed against citrullinated peptides may be present before the appearance of clinical symptoms of RA and constitute relevant diagnosis tools when present (3, 4). However, they are missing in about 30% of early disease, leading to some misdiagnosed cases of early RA (4) and can also be found in other conditions such as Sjögren's syndrome (5), psoriatic arthritis (6) or infectious diseases (7). Damage can occur within a few months of disease onset and the "missed" RA patients will then be at high risk of reduced functional capacity and lower quality of life.

Low back pain (LBP) is a common symptom in the general population in developed countries, where two thirds are reported to suffer from LBP at some point (8). This is also true for professional athletes where it seems to be more prevalent and related to the level of competition (9). Furthermore, it has been shown that the prevalence of physically disabling LBP is rising significantly with time (10) and generally declines with greater levels of education and increasing income (11). The prevalence of ankylosing spondylitis (AS), the prototype of the spondyloarthropathies (SpA) is between 0.2 to 1.0% (12). Low back pain may be related to SpA and in particular to ankylosing spondylitis (AS) in about 5% of cases (13) and athletes may have rheumatic diseases that may initially mimic sports-related injuries (14). The clinical presentation

of these diseases is typically delayed as patients tend to report their symptoms later, particularly in the absence of peripheral involvement such as arthritis or extra-articular manifestations (15). Low back pain tends to be managed mostly by primary care practitioners even in the presence of recurrent or persistent symptoms (16). Specialist referral is likely to be deferred particularly if initial investigations such as plain radiography fail to show any abnormalities. This may result in many cases not presenting until structural damage has occurred (17). This is particularly relevant since it is well known that clinical manifestations and disease activity measures are similar between patients with early non-radiographic axial SpA and those with AS presenting with radiographically defined sacroiliitis and/or syndesmophytes (18). Furthermore, a German study recently aimed to assess the prevalence and clinical features of psoriatic arthritis (PsA) and joint complaints in 2009 patients with psoriasis (19). Nineteen per cent of the patients had PsA, including not less than 4.2% patients with newly diagnosed diseases. This means that awareness has to be raised about the suitability of referring such patients earlier to the clinic.

Finally, there are several obvious research interests in building early inception cohorts that will allow to perform epidemiological studies, for example to assess which fraction of early patients with low back pain will go on to develop AS or PsA, and to collect data at baseline from these patients in order to find clinical, biological or even imaging markers of disease progression (20). This has been shown to be relevant in RA where early inception cohorts stemming from early arthritis clinics are providing invaluable information on our understanding of early undifferentiated arthritis. The identification of prognostic biomarkers may allow for the ultimate goal of early treatment to abort disease progression.

Previous experiences of early inflammatory clinics

There are different models of early inflammatory clinics (EIC) around the world, such as Berlin (21), Dallas (22), Leeds (23), Stockholm (24), Tokyo (25) and Vienna (26) that share the same concept of early disease definition and treatment (27). In the Leeds model a network of early arthritis clinics were created as part of the *Leeds Early Arthritis Project* (LEAP) (28). Patients are recruited from primary care referrals as well as from internal referrals such as the musculoskeletal service within the Leeds Teaching Hospitals NHS Trust, which enjoys unique access to primary care patients. These clinics were organized after an information campaign aimed to local general practitioners (GP), rheumatologists within the Yorkshire region (with a catchment area of over 4 million inhabitants) as well as colleagues from other related specialist areas. Furthermore, a regional register of newly diagnosed, consultant-confirmed diagnosis of RA patients was created: the Yorkshire Early Arthritis Register (YEAR). To be included, patients were required to have symptom duration of less than 12 months. Since the YEAR register was established in 1997, data have been captured in over 2,000 recently diagnosed RA patients (29). Under YEAR, patients are treated with standard therapy as determined by region wide agreed, best practice guidelines.

This set-up of early clinics allows therefore for the creation of inception cohorts of undifferentiated inflammatory arthritis. Previous work from Leeds followed a cohort of 100 patients with early undifferentiated arthritis of the hands showed that 30% of patient had persistent synovitis at 12 months requiring DMARD therapy with 15% of the whole cohort developing RA by 12 months (28).

In France, two large prospective cohorts have been reported. The VErA (*Very Early Arthritis,* n=314 (30)) cohort was created between 1998 and 2002 in two French regions (the Upper Normandy and the metropolitan area of Amiens which have a population of 1.800.000 and 300.000 people respectively), and the ESPOIR cohort (n=813), sponsored by the French Society of Rheumatology (31). Inclusion criteria for both cohorts included swelling of at least 2 joints that persisted for longer than 4 (VErA) or 6 weeks (ESPOIR) but had been evolving for less than 6 months. A clinical diagnosis of RA or of undifferentiated arthritis potentially becoming RA was required in the ESPOIR study. In the VErA cohort, all the private rheumatologists and those running rheumatology clinics in the five hospitals involved were encouraged to notify and refer all patients with inflammatory polyarthritis. To contact as many patients as possible, and to obtain a representative sample of these regions a large publicity campaign was conducted each year via the news, radio and TV media. However, despite a large information campaign, the median duration of the disease at inclusion was 4 months (30), indicating that awareness for early referral of patients to specialized early clinics still needs to be improved.

The Austrian Early Arthritis Registry was created in 1995 as part of the Austrian Early Arthritis Action (EAA) national initiative (32). It aimed at recruiting early inflammatory synovitis defined as two out of the following clinical criteria: joint pain and/or swelling in at least one joint, early morning stiffness >60 min in the absence of trauma with one laboratory criterion (positive rheumatoid factor, elevated ESR or CRP). Crucially the cut-point for symptom evolution is ≤12 weeks making this cohort a truly early group as by definition patients cannot fulfil the ACR criteria for the diagnosis of RA at such an early stage. Preliminary results at one year follow up showed that 65% of the patients had evolved into RA with another 15% remaining as undifferentiated arthritis. Despite no pre-defined treatment algorithm, 52% of the patients had a significant decrease in the DAS score with less radiographic progression. Furthermore, >50% achieved ACR50 responses within one year including some cases of spontaneous remission (32).

The majority of early EIC reported in the literature have described early RA cohorts. In the context of seronegative arthritis, the Leeds Early Inflammatory Back Pain clinic (LEIBPC) and the Oligoarthritis clinic (OLAC) were created between 1999 and 2000 as a research vehicle to allow for the creation

of inception cohorts of early SpA. Inclusion criteria for the LEIBPC which run monthly was a short duration (<12 months) of inflammatory back pain (using the Calin's criteria (33)). The OLAC (running every two weeks) took patients with a new onset (≤12 months) of peripheral oligoarthritis (defined as synovitic involvement of 4 or less joints). These clinics allowed for the recruitment of over 200 new patients over a 12 month period. Two major cohorts came out of these clinics. The oligoarthritis cohort allowed for the development of a treatment algorithm in early disease whereby intra-articular corticosteroids and DMARD therapy should be initiated without delay in the presence of persistent synovitis at 12 weeks from initial presentation (34, 35). Furthermore, a recent imaging and clinical assessment of our Early Back Pain cohort (36) at 8 year follow-up has allowed for the definition of HLA-B27 and the severity of MRI determined osteitis as important prognostic markers for the development of AS (37).

How are the EICs organized?

Although traditionally these clinics have been developed mainly on the setting of big academic departments, there are increasing numbers of district general hospitals now conducting EICs. These allow for a rapid assessment into secondary care as patients tend to be seen typically within 2 weeks of the initial referral. EICs are increasingly incorporating imaging methods such as ultrasound allowing for a comprehensive assessment within one hospital visit. Close links with allied care professionals such as physiotherapists, occupational therapist or podiatrists is paramount for a comprehensive approach to patient managements (38). The role of the clinical nurse specialist is increasing (39, 40), as they represent an integral part of the EIC not only for clinical input on education and management but also from the research standpoint.

A crucial aspect when setting up an EIC is the criteria for patient referral which must be well defined. A suitable early inflammatory clinic must be able to assess patients with an inflammatory arthralgia or arthritis within 1 to 2 weeks from symptom onset. Since a monoarthritis is -until proof to the contrary- potentially septic, such cases must be handled as potential emergencies and be referred for specialized advice accordingly. On the contrary, an oligoarthritis (inflammatory arthritis affecting no more than 4 joints) can be the onset presentation of RA and is the most common pattern of peripheral joint involvement in reactive arthritis (ReA), PsA, inflammatory bowel disease-associated arthritis and undifferentiated SpA. Oligoarthritis must therefore constitute a criterion for referral to an EIC. Furthermore, it must be remembered that persistent oligoarthritis in itself carries a high level morbidity (41, 42) and has a variable outcome which is favourably influenced by early and aggressive intervention (35).

Several referral recommendations for patients with inflammatory back pain (morning stiffness ≥30 minutes, pain at night or in the early morning and improvement with exercise (33) of short duration (<12 months), chronic LBP and suspected axial SpA are proposed. In this regard, one recommendation for the management of AS -developed using an evidence-based approach followed by expert consensus (43)- was to advise referral to a rheumatologist for further evaluation of possible AS any patients with chronic back pain that had persisted for longer than 3 months, features of inflammatory back pain and onset of symptoms before 45 years old. In Berlin (21), referral recommendations include LBP of at least 3 months duration in an individual younger than 45 years of age. Other referral criteria include fulfilment of inflammatory back pain criteria, and/or *HLA*-B27 positivity and/or radiographic evidence of sacroiliitis. These parameters were assessed over 18 months and allowed referral of 350 patients among a population of about 4 million people. The mean age of the patients reported was 40 years old, and nearly half of them were male. Interestingly, of those patients referred with only one of the suggested parameters being positive, inflammatory back pain was present in 36% whereas *HLA*-B27 was positive in 35%, and 18% of them had sacroiliitis on any imaging (21).

In addition, isolated enthesitis or joint pain associated with extra-articular features such as skin psoriasis, inflammatory bowel disease or uveitis should be referral criteria, in order to exclude the presence of subclinical joint involvement. The referral of a patient with isolated extra-articular involvement without joint pain must be discussed on a case to case basis, taking into account autoimmune status and imaging assessment.

Clinical assessments

Clinical history is recorded using standardized forms. This includes basic demographic as well as personal and family medical history of note. This is relevant regarding autoimmune disease since a significant risk of developing RA has been observed in the offspring of patients with AS (standardized incidence ratio (SIR): 2.96), Sjögren's syndrome (SIR: 2.25), Hashimoto thyroiditis (SIR 1.54), sarcoidosis (SIR 1.40) and psoriasis (SIR 1.36) (44). General clinical status (age, sex, comorbidity, smoking status and current medication) as well as occupation (with potential toxic exposure) is also recorded. The relevant measurement scales according to the patient's suspected disease need recording: Health Assessment Questionnaire (HAQ), Short Form Health Survey (SF36), Visual analogue scales of general health, disease activity and pain for RA; Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Functional Index (BASFI) for SpA. Tender and swollen joints count should be performed and reported in the form in order to calculate the disease activity score 28 (DAS28) in case of RA suspicion.

Complementary assessments

An informed consent of the early inflammatory clinics aims must be obtained from the patients, both for ethical principles and legislation. It is required before undertaking baseline genetic studies (*HLA* typing (12, 45), single nucleotide polymorphism assessments...) and can be the starting point to create a well-defined data set. Inflammatory markers (ESR, CRP) and a full blood count are required, as well as an initial

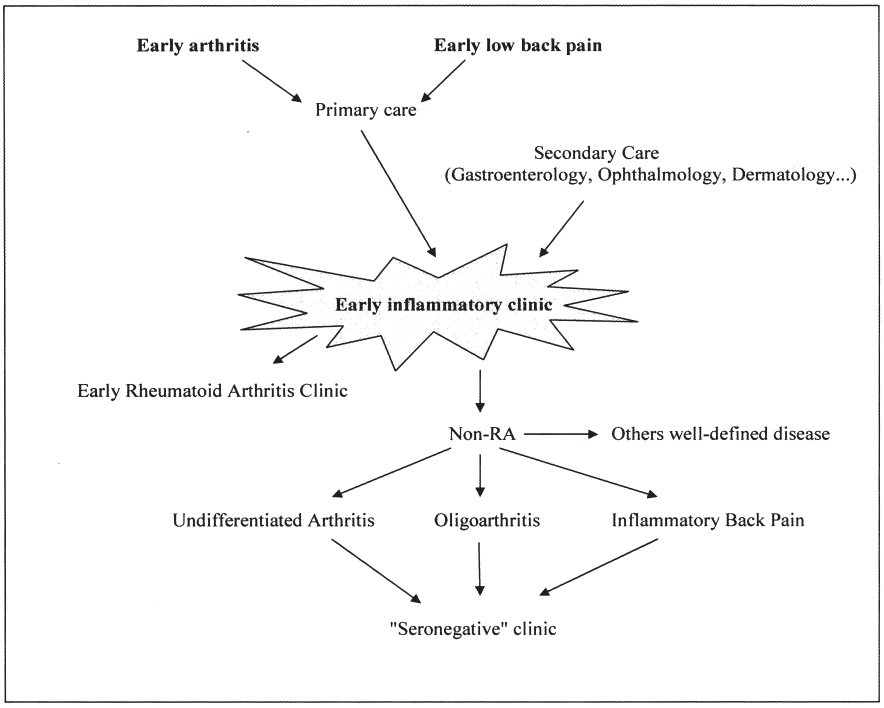

Fig. 1.

monitoring of the liver and renal functions. The procalcitonin level, since its usefulness remains discussed to discriminate between septic and non-septic early arthritis (46, 47), should be assessed. Viral (B and C hepatitis, EBV, HIV) status must be assessed, as well as *Chlamydia* serology since the causal role of synovial *Chlamydia* (*trachomatis* and *pneumoniae*) infections in patients with chronic undifferentiated SpA is well recognized (48). This is especially relevant because most of the patients with Chlamydia-induced reactive arthritis do not present with a typical Fiessinger-Leroy-Reiter syndrome associating arthritis, urethritis and conjunctivitis. An initial autoimmune screening should include rheumatoid factor (ideally of IgA, IgG and IgM isotypes (45)), second generation anti-CCP and antinuclear antibodies with antibodies directed to extractable nuclear antigens and double-stranded DNA if ANA positive. The assessments of the C3 and C4 fractions of the complement, blood cultures, angiotensin convertase, B and T cells, antineutrophil cytoplasmic antibody (ANCA) as well as an x-ray of the chest are also required in some cases. Radiographs of hands and feet, as well as spine, sacroiliac joints and hip in SpA patients, should be performed at the baseline assessment to bench mark the progression of the structural damage and hence help guide treatment. Other early assessments of the erosions and/or joint space narrowing by using ultra-sound (49) and MRI (50) may be included if available. Likewise arthroscopy of a swollen joint with synovial membrane study (51) has been undertaken but needs further evaluation before their use in daily practice is recommended.

Early treatment

In the case of the previously mentioned Leeds (LEAP) cohort, patients were completely naive to either corticosteroid or DMARD agents since immediate referral was organized. Likewise in the case of the VErA and ESPOIR cohorts, patients did not receive any disease-modifying anti-rheumatic drugs and/or corticosteroid therapy before inclusion (except if less than 2 weeks or intra-articular injection less than 4 weeks in the ESPOIR cohort) (31). In the YEAR register, preliminary results of comparing two standardized therapies on disease activity in early RA showed that a rapid escalation regime using methotrexate (7.5 mg weekly starting dose, escalated to 15mg and 20 mg weekly if no remission) did not change the outcome at 12 months when compared with a traditional approach (29). However, there is a need to define a standardized therapeutic model to be applied in all patients after diagnosis. There is now mounting evidence to suggest that the early use of biologic therapy for patients with RA within the 6 first months of the disease may lead to sustained remission (52). Larger longitudinal studies based on early cohorts will confirm whether this approach may indeed lead to the permanent arrest of disease. Likewise, research in SpA is currently focusing in the early and active treatment of patients with inflammatory back pain (53, 54) in order to prevent structural disease progression and avoid deformity The efficiency of infliximab for reducing clinical and imaging evidence of disease activity and to induce significant reduction in inflammatory biomarkers level (IL-6, VEGF and CRP) has thus been showed in patients with AS (55) and notably with early MRI-diagnosed sacroiliitis

Conclusion

Early inflammatory clinics are needed to assess patients with arthritis of recent onset as well as those suffering from inflammatory back pain as early in their disease process as possible. The benefit for the patient will be the rapid implementation of an efficacious and safe evidence based treatment regime aiming to avoid disease progression and ultimately to induce remission. Furthermore the data collected within these clinics will help define the different genotypes and phenotypes of disease which will contribute to a better understanding of disease pathogenesis. This in turn will help to define the most appropriate treatments for each patient at every stage of disease.

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