TREATMENT IN THE PRE-ARTHRITIS PHASE

Experimental studies on murine models of arthritis suggest that initiating treatment before arthritis development could be more effective. A meta-analysis from 2017 of 16 studies has proven that initiating DMARD therapy in the induction phase of arthritis, before the development of clinical arthritis and of autoimmunity, had beneficial effects on the severity of the arthritis. The most solid evidence was for methotrexate and abatacept [10]. Treating has been effective even on murine models with antibodies presence, but without clinical arthritis. There are no head-to-head trials, but at this subtype, murine models with antibody presence, methotrexate seemed more effective than anti-tumor necrosis factor blockers. These experimental studies have had a lot of limitations, the most relevant being the fact that the treatment period has been extended in the clinical arthritis phase and the primary objective was arthritis severity, not arthritis development. The trend in this animal studies favors initiating treatment in the pre-arthritis phase, but there is the need for bigger head-to-head studies, limited on the pre-arthritis phase period, in which different treatments, like methotrexate and abatacept be compared in order to obtain more valuable information [11].

In 2009, the first placebo-controlled trial, that evaluated initiating treatment in the pre-arthritis phase, was published and it demonstrated that two intramuscular injections of dexamethasone in seropositive arthralgia patients, decreased autoantibody levels but did not prevent the development of arthritis [12].

In 2016, the PRAIRI trial (prevention of clinically manifest RA by B cell directed therapy in the earliest phase of the disease) demonstrated that a single infusion of rituximab in seropositive patients with arthralgia and any sign of systemic and/or local inflammation delayed, but did not prevent, the development of clinical arthritis [13].

Currently there are more ongoing studies that have the primary objective to prove this concept with different subpopulations and treatments, but most of them have inclusion criteria based on the presence of autoantibodies. The publication of this trials results in the next decade will help to better understand the efficacy of therapeutic intervention with the scope of preventing chronic arthritis and what subset of patients at risk to treat.

There are no recommendations for management of CSA, but current practice is symptomatic treatment with non-steroidal anti-inflammatory drugs, pain relievers and of course monitoring [11].

The APPIPRA study (arthritis prevention in the pre-clinical phase of RA with abatacept: a multi-center, randomized, double-blind, parallel-group, placebo-controlled clinical trial protocol) included patients with non-traumatic arthralgia who are auto-antibody positive (either positive for RF and ACPA or have high levels of ACPA) had as a primary outcome the development of either clinical arthritis or RA. The intervention was represented by Abatacept 125 mg weekly over twelve months [14].

The ARIAA trial, had the same intervention, Abatacept weekly over six months, and included patients who are positive for ACPA and have subclinical inflammation in the dominant hand, detected by MRI. The primary end point was improvement of inflammation [11].

TREAT Early Arthralgia to Reverse or Limit Impending Exacerbation to Rheumatoid arthritis (TREAT EARLIER): a randomized, double-blind, placebo-controlled clinical trial protocol included patients with CSA and recent-onset arthralgia (< 1 year) that is suspect to progress to RA according to the expertise of the treating rheumatologist and need to have subclinical inflammation of the hand or foot joints at 1.5 T MRI. Intervention will be randomly assigned and includes a single-dose of intramuscular 120 mg methylprednisolone followed by methotrexate (increasing dose to 25 mg/week orally) or placebo (both; injection and tablets) over the course of 1 year. Thereafter, participants are followed for another year. The primary endpoint is the development of clinically detectable arthritis, either fulfilling the 2010 criteria for RA or unclassified clinical arthritis of ≥ 2 joints, which persists for at least 2 weeks. DMARD-free status is a co-primary endpoint. It will test the hypothesis whether intervention in patients in this early phase with the cornerstone treatment of classified RA (methotrexate) hampers the development of persistent RA and reduce the disease burden of RA [15].

The STAtins to Prevent Rheumatoid Arthritis (STAPRA) trial included auto-antibody positive patients who received atorvastatin 40 mg daily for 36 months had as a primary outcome the development of clinically detectable arthritis. the trial was prematurely stopped due to a low inclusion rate, mainly because of an unwillingness to participate [16].

In 2016, the StopRA trial begun. It included ACPA positive patients without inflammatory arthritis, who were recruited from health fairs or rheumatology clinics and who were first degree relatives of patients with RA. The intervention was hydroxychloroquine 200-400 mg a daily, over 12 months. The outcome was represented by development of clinically apparent RA.

Risk stratification is essential in order to advance studies in preventing RA. Adequate risk stratification is crucial in the design and interpretation of prevention studies. The trials strength is considerably influenced by each individual's risk from the

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