Clinical aspects of rheumatoid arthritis: highlights from the 2010 ACR conference (Part II)

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This is the second part of two articles on the 2010 annual scientific meeting of the American College of Rheumatology (ACR) that was held in Atlanta, GA, USA, on 7–11 November 2010. The first part highlighted abstracts on the new classification criteria for rheumatoid arthritis (RA) and on predictors of disease severity, laboratory tests and imaging studies in early RA [1]. This article will review the major abstracts on remission and treatment with emphasis on the safety data for biologic therapies.

Remission

Remission is increasingly accepted as the primary target of treatment of RA. There are several definitions for remission and these include the ACR criteria proposed in 1981, the European League Against Rheumatism (EULAR) criteria and the US FDA criteria [2,3,101]. Recently, the ACR and the EULAR, aided by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) initiative, developed new criteria for remission in RA [4]. While a discussion on these criteria is beyond the scope of this article, remission may simply be defined as the complete suppression of the inflammatory process.

Disease remission in RA may also be defined clinically as the absence of evidence of disease activity. As discussed in part I of these articles ultrasound and MRI studies have demonstrated the presence of inflammatory changes in patients in clinical remission. We therefore sought to examine if patients in ACR remission (1981 criteria) had evidence for persistent inflammation on histology, ultrasound and MRI [5]. A total of 13 synovial specimens obtained from 12 patients, in ACR remission, were scored for hyperplasia of synovial lining and synovial stroma, inflammation, lymphoid follicles and vascularity on a scale of 0–4. The total scores were classified as minimal (0–5), mild (6–10), moderate (11–15) or severe (16–20) disease activity. An ultrasound and/or MRI of the joint scheduled for surgery, was done when possible and if indicated. Three specimens had severe, six moderate, two mild and two minimal disease activity on histology. Interestingly, the three out of four specimens with minimal and mild disease were subjects on anti-TNF therapy while the other was on methotrexate. Synovitis was seen in all nine patients that had ultrasound imaging and in all four available MRI scans. Our study demonstrated evidence for persistent disease activity on histology and imaging studies in patients in clinical remission and may explain the mechanism for radiographic progression in patients in clinical remission.

Radner *et al.* tackled the question of whether it was meaningful from a socioeconomic point of view to aim for remission in patients with low disease activity (LDA) [6]. An analysis of 356 patients with established RA revealed that when patients in remission were compared with those with LDA, significant differences were noted in utility which was assessed using the short form 6D (SF-6D), physical disability as assessed by the health assessment questionnaire (HAQ) and productivity as assessed by work productivity and activity impairment. Disease activity was measured using the Clinical Disease Activity Index (CDAI). Preliminary longitudinal studies showed significant differences in the above outcomes over 1 year between the two groups: SF-6D of 0.89 versus 0.80, HAQ of 0.22 versus 0.69 and overall work impairment of 12.2 versus 31% for remission versus LDA, respectively. This study supports the concept that aiming for remission should be the target and is superior even to LDA states.

Shahouri *et al.* determined the rates of remission, based on the new ACR/EULAR criteria, in a large multicenter RA clinical practice [7]. The overall rate of remission in the community using contemporary RA treatment was between 5.1 and 7.5%, rates that are substantially lower than

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seen in clinical trials using the Disease Activity Score in 28 joints (DAS28) criteria. Vermeer *et al.* reported on a similar study of subjects from the Dutch RA Monitoring (DREAM) remission induction cohort [8]. A total of 534 newly diagnosed early RA (symptoms less than 1 year) patients were treated to a DAS28 target of <2.6 with a medication protocol that comprised methotrexate, sulfasalazine and/or anti-TNF agents. The cohort comprised 56.6% rheumatoid factor (RF) positive and 62.4% anti-cyclic citrullinated peptide (anti-CCP) positive subjects with symptom duration of 15 weeks and a baseline DAS28 of 5.0. Data were available for 210 patients at 2 years and showed that 64.3% patients achieved DAS28 remission and 54.4% the ACR remission criteria. These studies indicate that long-term remission is a realistic goal in RA.

Loppin *et al.* determined remission rates in real-life settings [9]. Remission (DAS28 less than 2.6) rates were assessed in 364 RA patients receiving usual care. Results were available for 328 patients of whom 79.3% were RF positive and 73.8% anti-CCP positive with a mean disease duration of 13.6 months. The rate of global remission was 28%. Multivaraiate analysis showed that RF status, male sex, younger age and absence of concomitant prednisone use were associated with the rates of remission. Remission rates were 15% for those not on DMARDs, 24% with DMARDs and 47% with anti-TNF therapy. A Mexican study addressed the ability to achieve sustained remission in a group of early RA patients treated with conventional DMARDs [10]. The 101 subjects in the study comprised 78 RF positive and 71 CCP positive patients with a mean disease duration of 5.2 months. A total of 71 patients had aggressive therapy with three or more DMARDs. At 2 years, 34 patients achieved permanent sustained remission (PSR) defined as DAS28 of ≤2.4 on at least three consecutive visits 2 months apart and maintained until last visit, 54 patients achieved lost sustained remission (LSR), where patients achieved remission but were unable to maintain status at the follow-up visit, while 13 had persistent disease activity. Patients with PSR and LSR were less likely to be seropositive and had lower baseline clinical scores. Early sustained remission, within the first year, was the only predictor of PSR. Another study from Canada aimed to assess the frequency and predictors of sustained remission [11]. Analysis was done on 851 patients from a cohort of 994 patients with early RA (symptoms between 3 and 12 months) that comprised 61% RF positive and 43% anti-CCP positive subjects with a mean disease duration of 170 days. Remission was defined as a DAS28 of less than 2.6 and sustained remission as consecutive remission at years 1 and 2. DMARDs were used in 74, 90 and 87% of patients at baseline, 1 year and 2 years, respectively, while 2, 15 and 23% were on biologic at baseline, 1 year and 2 years respectively. Remission at year 1 or year 2 was seen in 28%, but only 8% were with sustained remission. Univariate logistic regression revealed that low baseline DAS28, HAQ, disease duration and C-reactive protein (CRP) were significant predictors for sustained remission. Taken together these studies also show that disease duration, low disease activity at baseline and choice of therapy may be predictors for achieving remission.

In summary, the above studies show that remission is an achievable goal especially with the use of biologic therapies. While remission was shown to be superior to LDA based on socioeconomic aspects, histological and imaging studies highlighted the persistence of inflammation in patients deemed to be in clinical remission. In addition to early therapy, low disease activity at baseline and attainment of early remission appear to be predictors for sustained remission.

Treatment

Treatment strategies for RA have evolved over the past two decades as the pathophysiology of the disease becomes unraveled and more data emerge on the safety of currently available therapies. Further paradigm changes will occur with the development of new drugs for RA. While the biologic therapies have changed the landscape of RA management there remains an important role for the use of DMARDs in the treatment of RA. The following section will highlight the abstracts on treatment of RA with a focus on safety of biologic therapies.

Methotrexate

Methotrexate is the most commonly used DMARD for treatment of RA. The excellent efficacy versus toxicity ratio of methotrexate supports the common practice of its use as the first DMARD in the majority of patients with RA. Despite the use of this medication for the past several decades there is no consensus on optimal dosing or route of administration. There is emerging data to suggest that parenteral methotrexate at doses of 20 mg or more weekly may be the optimal initial treatment of choice for early RA [12]. Bykerk *et al.* presented their experience

on the use of parenteral methotrexate from the Canadian early Arthritis Cohort (CATCH), a multicenter observational prospective 'real-world' cohort for patients with early inflammatory arthritis [13]. A total of 593 patients with DAS 28 of 2.6 or more and with available data at 6 and/or 12 months were selected from a total of 898 subjects. It was noted that patients receiving early parenteral methotrexate were more likely to achieve LDA states (67 vs 52%) and DAS28 <2.6 (53 vs 40%) compared with patients receiving all other regimen, within the first year ($p < 0.05$). Stamp *et al.* revealed that it took at least 6 months for the long chain polyglutamates to reach 90% steady state after changing from oral to subcutaneous administration of methotrexate emphasizing that adequate time must be allowed to determine clinical response to a change in route of administration [14]. Welsing *et al.* used complex statistical methods on data from the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) trial and calculated the optimal effective dose of methotrexate to be 15 mg a week, in patients with early RA [15].

The outcome of patients with a good initial response to methotrexate, from the Swedish Pharmacotherapy (SWEFOT) trial, was explored at 2 years [16]. A total of 487 patients with early RA (symptom duration of less than 1 year) were started on methotrexate at a rapidly escalating dosage up to at least 20 mg a week. After 3–4 months, most of the 147 patients who had a DAS28 of 3.2 or less were continued on methotrexate and were followed in 'regular care' with 3-monthly assessments. Complete data at 24 months were available for 65% of patients. At the 6, 12, 18 and 24 months time points, 61.1, 61.0, 64.2 and 72.7% of patients, respectively, were in DAS28 remission, and 82.1–87.6% in a LDA state. The mean progression for the total Sharp–van der Heijde score at 24 months was 3.90. The mean radiographic progression for the subset of patients who had been in sustained remission at each time point from 3 to 24 months (18 patients) was 4.06. Progression in patients on methotrexate monotherapy throughout follow-up was 3.97. This study shows that although an initial good response to methotrexate appears to portend a good clinical prognosis, radiographic progression appears to continue even in those in clinical remission. Taken together the above studies show that parenteral methotrexate, starting at a dose of 15 mg a week may be an optimal approach for the treatment of RA but these patients need to be closely monitored for radiographic progression.

Anti-TNF therapies

There now is a large body of evidence to demonstrate the efficacy of treating RA with anti-TNF therapy, usually in combination with methotrexate. The use of these medications however has resulted in a number of safety concerns with the risk for infections and neoplastic diseases being of particularly high importance [17,18]. Data from national registries and meta-analyses of clinical trials have helped provide long term safety information.

Winthrop *et al.* used validated algorithms to identify cases of nontuberculous (NTB) mycobacterial infections and tuberculosis (TB) from a large US cohort [19]. They report 24 cases of NTB infections and less than 11 cases of TB among 29,500 RA patients that had recently been started on anti-TNF therapy. The calculated incidence rates were 66.7 and 45.9 per 100,000 patient-years for NTB and TB respectively, and compares with a rate of 5.1 per 100,000 for TB in the general US population. This study emphasizes the need to screen for latent TB prior to starting anti-TNF therapy. Galloway *et al.* reported on the rates of herpes zoster (HZ) in RA patients treated with anti-TNF agents or nonbiologic DMARDs and to compare the rates for the individual anti-TNF agents, based on analysis of data from the British Society for Rheumatology Biologics register [20]. The anti-TNF treated cohort was recruited alongside a comparator group with active disease (DAS28 >4.2) treated with DMARDs. A total of 322 HZ infections occurred in the anti-TNF cohort (incidence ratio [IR] of 7.8/1000 patient-years) and 46 in the DMARD cohort (IR: 4.0/1000 patient-years) and the adjusted hazard ratio for HZ was 2.2. The HZ infections were also more severe among those on anti-TNF therapy. The risk pattern was similar between the different anti-TNF agents.

The number of infections and malignancies in RA patients treated with anti-TNF therapies are typically confounded by other therapies and comorbidities associated with long standing RA. Thompson *et al.* investigated the risk for infections in early RA patients who were naive to DMARD/methotrexate therapy and were started on anti-TNF therapies [21]. A systemic literature review of data extending to mid-2009, yielded six randomized, double-blind, placebo controlled trials that met inclusion criteria. These trials comprised 2183 patients on biologic therapy and 1236 on control therapy. The pooled odds ratio for infections and malignancies were 1.16 and 1.07, respectively, suggesting no increased risk for these adverse events in this specific subset of RA patients.

Le Blay *et al.* conducted a systemic review of the literature on malignancy in RA patients treated with anti-TNF agents [22]. A total of 25 articles and two abstracts were selected for analysis from 641 articles and 110 abstracts retrieved from the initial search. Based on the registries which comprised 40,128 patient-years in the anti-TNF group and 59,862 in the DMARD group, the pooled odds ratio for malignancy was 0.81. The standardized IR for malignancies, versus the general population for three long-term extension studies ranged from 0.84 to 1.07, and for four of the registries was 0.74 to 1.36, none being statistically significantly higher than 1. Burns *et al.* conducted a meta-analysis to determine whether the use of biologic therapies in RA is associated with an increased risk for lymphoma [23]. A literature search of randomized controlled trials in RA patients of at least 12 week duration with clearly defined lymphoma outcomes, between January 1990 and May 2010, was conducted. These results were then combined with previous meta-analysis assuming the reported cancer risk (odds ratio 3.3) as the lymphoma risk. The search produced 11 articles of which four satisfied the initial search criteria. A total of 19,322 patients and 119,433 person years of follow-up and 129 cases of lymphoma were identified. The mean disease duration was 127–158 months The pooled risk for lymphoma was estimated to be 1.20. Combining with a recent meta-analysis did not change the pooled risk estimate (1.22) and showed no increased risk for lymphoma with biologic use in RA. The above abstracts suggest that the risk for malignancies including lymphomas in patients treated with anti-TNF agents may be lower than previously estimated. However, continuation of the long-term studies is warranted to address the question on the risk for malignancies in RA patients on anti-TNF therapies. The studies confirm that the risk for TB, NTB and HZ are increased in patients on anti-TNF therapies compared with the general population and to RA patients on DMARDs.

Switching from anti-TNF therapies to other biologics

The anti-TNF agents are often used as the first line of biologic therapies in patients who fail to respond adequately to the traditional DMARDs. Up to 50% of patients on anti-TNF agents however, do not respond, lose efficacy or develop adverse events leading to their discontinuation. The optimal next drug of choice is still a matter of debate and was explored by several investigators. Many countries require the use of at least two DMARDs before starting patients on to biologic therapies. Lie *et al.* used the Norway DMARD (NOR-DMARD) registry to examine the value of switching from methotrexate monotherapy to methotrexate and DMARD combinations before switching to methotrexate and anti-TNF versus switching directly from methotrexate monotherapy to methotrexate and anti-TNF therapy, in patients with RA of less than 5 years [24]. In patients who were methotrexate failures, methotrexate and anti-TNF was superior to methotrexate and DMARDs in terms of disease states reached, response and remission rates and retention to therapy. Furthermore, the subgroup of patients receiving methotrexate and anti-TNF after taking methotrexate and DMARD combination reached less favorable disease activity states and a lower remission rate than patients receiving methotrexate and anti-TNF after having failed methotrexate only.

The utility of a switching to a second anti-TNF agent was assessed by Goran *et al.* [25]. They analyzed data on 399 patients from a US cohort who switched to a second biologic agent. Of these 215 switched to a second anti-TNF agent, 148 changed medication due to lack of response, 31 for intolerability and 36 for other reasons. Significant improvements were noted in tender joint scores, swollen joint scores, erythrocyte sedimentation rate, CRP and disease severity for those who switched to the second anti-TNF agent due to failure of initial anti-TNF agent, or switched due to intolerability. However, Kekow *et al.* showed that use of rituxan may be superior to treatment with a second TNF blocker in those who have failed the fist anti-TNF agent [26]. This was a noninterventional, retrospective study of 196 patients who had received etanercept, adalimumab or infliximab. After 6.6 months treatment, the mean DAS28 reduction was significantly greater in the rituximab group (n = 90) when compared with patients treated with a second TNF blocker. The difference was even more impressive in the anti-CCP positive patients. An analysis of data from the Stockholm (Sweden) registry also tried to determine whether patients who had failed one or more anti-TNFs achieved better results when switching to another anti-TNF or when switching to rituximab [27]. In this registry, a total of 850 patients had switched to an alternative biologic agent, 679 to another anti-TNF agent and 171 to rituximab. A mean reduction of 1.79 and 1.37 in DAS 28 measures was seen for rituximab and anti-TNF agents, respectively. Interestingly, the improvement was significantly

more in those who switched to rituximab compared with those who switched to monoclonal antibodies and when the reason for discontinuation was intolerance. A study from Spain also showed similar results and these findings are in keeping with results of the Randomized Evaluation of Long-term Efficacy of Rituximab in RA (REFLEX) trial [28,29]. These studies show that patients who fail an anti-TNF agents can gain clinical benefits regardless of whether they are switched to another anti-TNF agents or to rituximab but rituximab appears to provide slightly better overall results than a change to another anti-TNF agent.

B-cell depleting therapies

Scientific literature over the past decade has demonstrated that medications that target B cells can be effective in the treatment of RA [30]. Data on the safety of rituxan and reports on the efficacy of newer agents that target B cells were presented at the conference. A report of the long term safety of rituximab was presented by van Vollenhoven *et al.* [30]. The analysis included 3189 patients providing 9342 patient-years of exposure to rituxan. The most frequent adverse event was infusion related reactions with most occurring after the first infusion. The overall serious infection rate was 4.35 events/100 patient-years which was comparable to that observed in the placebo population (3.19/100 patient-years). This study shows that rituximab remains generally well tolerated over time and over multiple courses, with a safety profile similar to that of the pooled placebo population.

Ocrelizumab is a humanized, monoclonal anti-CD20 antibody and its use may be associated with less complement-dependent cytotoxicity and enhanced antibody-dependent cell-mediated cytotoxicity [31]. Rigby *et al.* [32] reported on the ongoing Phase III, multicenter, randomized, placebo-controlled, parallel study of ocrelizumab and methotrexate compared with methotrexate monotherapy in patients with active RA. In this study of 1015 RA patients with active disease (defined as more than four tender and four swollen joints, with a CRP greater than 0.6 mg/dl) on a stable dose of methotrexate, were randomized to receive placebo, two doses of ocrelizumab 200 mg or two doses of ocrelizumab 500 mg (days 1 and 15 and weeks 24/26) with 100 mg of methyprednisolone as premedication. The primary end points of ACR 20 at weeks 24 and 48 were met by ocrelizumab, and were significantly more than with placebo. The secondary end points of ACR 50/70 and the inhibition of progression of joint damage as assessed by the van der Heijde-modified total Sharp score were also significantly more in the ocrelizumab groups. Serious adverse events and overall infections were similar in both groups but serious infectious events were more frequent with the ocrelizumab 500 mg group. This study suggests that ocrelizumab may be an effective agent for the treatment of seropositive RA. Tak *et al.* reported on the Phase III randomized, double-blind, placebo-controlled study of ocrelizumab with methotrexate or leflunomide in patients with active RA who had an inadequate response to one or more anti-TNF inhibitor [33]. The patients on active medication group showed statistically significant improvements in ACR 20/50/70 scores at weeks 24 and 48 compared with placebo. A significant reduction in radiographic progression was again noted only in the ocrelizumab group. Serious infections were more frequent in ocrelizumab group. These studies show that B-cell depletion therapy may be a safe and effective treatment option for the RA.

Other biologics

Hochberg *et al.* presented an integrated analysis of safety data on long term use of abatacept [34]. Data from eight RA trials with abatacept included 4149 patients with 12,132 patient-years of exposure, with a mean exposure of 35.6 months. The cumulative incidence rates for hospitalized infections for the 7-year period was 2.64 per 100,000 patient-years and the annual incidence rates per 100,000 patient-years for serious adverse events did not increase with increasing abatacept exposure for the 7-year period. The incidence rates for nonmelanoma skin cancer and solid tumors in the cumulative period were 0.73 and 0.59 per 100 patient-years, respectively. Gottenberg *et al.* reported on the risk for severe infections in RA patients treated with abatacept from the French registry [35]. The Orencia and Rheumatoid Arthritis registry collects data on RA patients on orencia at baseline, 3 and 6 months and then every 6 months. Data was available for 1036 patients, with a median disease duration of 12 years and 557 patient-years of follow-up. The rate of severe infections was calculated to be 5.6 severe infections/100 patient-years and serious infections occurred at a median duration of 4.6 months after start of abatacept therapy. No opportunistic infection was observed. Multivariate analysis on 709 patients revealed that a history of cancer, record of severe infections and diabetes were significantly associated with a higher risk for severe infections.

Keystone *et al.* reported on the safety, immunogenicity and maintenance of efficacy in patients who switched from long-term IV abatacept to subcutaneous abatacept formulation [36]. In this open label, single-arm trial patients on abatacept from the Abatacept in Inadequate Responders to Methotrexate (AIM) or Abatacept Trial in Treatment of Anti-TNF Inadequate Responders (ATTAIN) trials were recruited to switch to self-administered subcutaneous abatacept 125 mg/week. In total, 123 patients entered the study with a mean DAS28 of 3.4. By month 3, adverse events were reported in 39.8% patients overall. The proportions of patients achieving low disease activity states and remission was sustained after switching from IV to subcutaneous abatacept. These studies demonstrate that there was no increase in risk for infection rates with an increase in exposure to abatacept (for up to 7 years) and that switching patients from intravenous to subcutaneous abatacept is well tolerated without compromising efficacy.

Genovese *et al.* reported on the safety and tolerability of tocilizumab in long-term extension studies of rheumatoid arthritis [37]. Pooled data from clinical trials and ongoing extension studies yielded a total of 4009 patients who received tocilizumab with a median treatment duration of 3.1 years and a total observation time of 10,994 patient-years. The rates for adverse events, serious adverse events and rate of malignancies were 321.1, 14.6 and 0.8 per 100 patient-years, respectively, and suggest that the longer-term safety profile of tocilizumab is not different from that established in the Phase III studies. Infections were the most frequent adverse events and serious adverse events.

Conclusion

The annual meeting of the ACR continues to be the premiere meeting in rheumatology. Scientific material on remission demonstrated the importance to aim for remission, the feasibility of achieving remission and evaluated the predictors for remission in the management of RA. Several abstracts reported on the long term safety of biologic therapies in the treatment of RA. The information presented at the meeting will hopefully help the clinician provide better and safer treatment strategies for our patients.

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