The treatment of spondyloarthropathies

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Summary

Psoriatic arthritis belongs to the family of spondyloarthropathies which also includes undifferentiated ankylosing spondylitis, ankylosing spondylitis, juvenile SpA, arthritis associated with ulcerative colitis or enteroarthritis, reactive arthritis and anterior uveitis. The presentation will be focused on the classification of spondyloarthropathies as well as the treatment of these diseases. With regard to this, recommendations issued by EULAR (European League Against Rheumatism) and SIR (Italian Society of Rheumatology) on the treatment of Psoriatic Arthritis will also be discussed. Moreover, the results from an Italian multicenter study will be presented for the first time; more than 3000 patients were enrolled in this study and were followed over the last 5 years. Patients had different forms of arthritis. Moreover, the preliminary results from a study conducted at the University Hospital in Siena will be briefly presented; 241 patients with spondyloarthritis – mostly psoriatic – and ankylosing spondylitis were enrolled in this study. Then, attention will be brought to the issue of the treatment of initial forms of spondyloarthropathies and the results from some studies on anti-TNF-alpha drugs will be presented. Finally, the issue of anti-TNF-alpha drug immunogenicity and the consequences that the production of anti-drug antibodies may have on the efficacy and safety of the drugs will be discussed.

KEY WORDS: spondyloarthropathies; psoriatic arthritis; therapy; biological agents.
symmetric arthritis of metacarpophalangeal, proximal interphalangeal joints and can be seen in 17% of cases. In this cases, a correct diagnosis is crucial because the anti-citrullinated cyclic peptide antibodies (anti-CCP), which are thought to be specific to rheumatoid arthritis, can also be found in this forms of psoriatic arthritis. Both rheumatoid arthritis and psoriatic arthritis are relatively frequent diseases (0.5% of the population suffers from rheumatoid arthritis, while the proportion of patients suffering from psoriatic arthritis is a little higher) and concomitance of psoriasis and rheumatoid arthritis is not rare. Therefore, when we have a rheumatoid-like form with positive anti-CCP, it is important to perform a differential diagnosis, without excluding the possible concomitance of the two patterns; in these cases, there are virtually no differences in these forms from the therapeutic point of view. **Asymmetric oligoarthritis with dactylitis belongs to a different field:** these forms often do not show any real joint involvement, but dactylitis is clinically characterized by “sausage digits”; however in some cases joint involvement can also be concomitant to synovitis, but several patients only have dactylitis. **Ankylosing spondylitis with or without peripheral involvement,** usually associated with HLA-B27 accounts for 8% of our patients with psoriatic arthritis. 

Is there a different therapeutic approach within this range? Yes, because the availability of anti-TNF agents let us go beyond this classification. It is not possible to include exclusively enthesopathic or enthesitic psoriatic arthropathy because some patients complain of pain, invalidating pain, to the spine, the joints, and we should always remember that in the absence of arthritis, there could be an enthesitis – even diffused – that can be as invalidating as arthropathies. For years, these patients were neglected because they were considered as having fibromyalgia, while today by using ultrasound imaging – a great advance for rheumatologists from the diagnostic point of view – it is possible to demonstrate not only the presence of enthesitis (which can be severe in some cases from the clinical point of view also for their extension) but also of isolated dactylitis. These are two conditions that can result into relevant invalidity to patients and that should be also considered in the treatment with biological agents, as it is the case in the moderate form. 

From the therapeutic point of view, clinical experience has shown two main groups of arthritis: mainly spondylitic forms, which usually respond poorly to methotrexate and corticosteroids, and peripheral psoriatic arthritis with variable clinical response to drug treatment. 

With regard to the specific use of anti-TNF, it has not been demonstrated that one specific anti-TNF should be preferred to another in the initial phase, and the choice in the clinical practice cannot be done without taking into consideration comorbidities and concomitant medications. The speaker stated that, in his opinion, in case of arthropathy associated with chronic bowel diseases (not only in psoriatic arthritis) inflix-
Figure 3 - Recommendations of the Italian Society of Rheumatology for the use of biological agents in psoriatic arthritis.

**RECOMMENDATIONS OF THE ISR FOR THE USE OF BIOLOGICAL AGENTS IN AP**

<table>
<thead>
<tr>
<th>INCLUSION CRITERIA</th>
<th>EFFICACY ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PA with peripheral involvement</strong></td>
<td><strong>PA with peripheral involvement</strong></td>
</tr>
<tr>
<td>Lack of response to NSAIDs and to 1 DMARD for at least 3 months. At least 2 local injections of steroids in case of mono or oligoarthritis</td>
<td>From therapy initiation until 3, 6 months and then yearly</td>
</tr>
<tr>
<td><strong>PLUS</strong></td>
<td>Polyarthritis → ACR50 response</td>
</tr>
<tr>
<td>Presence of arthritis in at least one joint</td>
<td>Mono-oligoarthritis → reduction ≥ 50% on pain VAS</td>
</tr>
<tr>
<td>Pain VAS ≥40 mm</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>HAQ-DI ≥0,5</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

Figure 4 - Update of the Recommendations of the Italian Society of Rheumatology on the use of biological agents in psoriatic spondylitis.

**UPDATE OF THE RECOMMENDATIONS OF THE ISR ON THE USE OF BIOLOGICAL AGENTS IN AP**

<table>
<thead>
<tr>
<th>INCLUSION CRITERIA</th>
<th>EFFICACY ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psoriatic arthritis</strong></td>
<td><strong>Psoriatic arthritis</strong></td>
</tr>
<tr>
<td>Sacroiliitis and/or spondylitis</td>
<td>Sacroiliitis and/or spondylitis</td>
</tr>
<tr>
<td>Lack of response to 2 NSAIDs for at least 3 months</td>
<td>From therapy initiation until 3, 6 months and then yearly</td>
</tr>
<tr>
<td><strong>PLUS</strong></td>
<td>BASDAI improvement &gt;50%</td>
</tr>
<tr>
<td>BASDAI ≥40 mm</td>
<td>20 mm on a VAS scale 0-100</td>
</tr>
<tr>
<td>Expert opinion</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

Figure 5 - Update of the Recommendations of the Italian Society of Rheumatology on the use of biological agents in psoriatic arthritis characterized by enthesitis.

**UPDATE OF THE RECOMMENDATIONS OF THE ISR ON THE USE OF BIOLOGICAL AGENTS IN AP**

<table>
<thead>
<tr>
<th>INCLUSION CRITERIA</th>
<th>EFFICACY ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PA characterized by enthesitis</strong></td>
<td><strong>PA characterized by enthesitis</strong></td>
</tr>
<tr>
<td>Lack of response to NSAIDs and to 1 DMARD for at least 3 months. At least 2 local injections of steroids</td>
<td>From therapy initiation until 3, 6 months and then yearly</td>
</tr>
<tr>
<td><strong>PLUS</strong></td>
<td>Reduction</td>
</tr>
<tr>
<td>Painful enthesitis at pressure ≥ 2 on a Likert scale 0-4</td>
<td>≥ 50% on pain VAS</td>
</tr>
<tr>
<td>Pain VAS ≥40 mm</td>
<td>≥ 20% MASES</td>
</tr>
<tr>
<td>HAQ-DI ≥0,5</td>
<td>(at least 3 sites with enthesitis at baseline)</td>
</tr>
<tr>
<td>Expert opinion</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>
The treatment of spondyloarthropathies

UPDATE OF THE RECOMMENDATIONS OF THE ISR ON THE USE OF BIOLOGICAL AGENTS IN AP

INCLUSION CRITERIA
PA characterized by dactylitis

Lack of response to NSAIDs and to 1 DMARD for at least 3 months. At least 2 local injections of steroids

PLUS
Painful dactylitis at pressure (≥ 2 on a
Likert scale [0-4])

Pain VAS ≥40 mm
HAQ-DI ≥0.5

Efficacy Assessment
PA characterized by dactylitis

From therapy initiation until 3, 6 months and then yearly

Reduction
≥ 50% on pain VAS

≥ 20% number of digits with dactylitis
(at least ≥ 5 digits with dactylitis at baseline)

Expert opinion

EULAR recommendations for the management of PsA, with levels of evidence, grade of recommendations

Recommendations
1. In patients with psoriatic arthritis, non-steroidal anti-inflammatory drugs may be used to relieve musculoskeletal signs and symptoms.
2. In patients with active disease (particularly those with many swollen joints, structural damage in the presence of inflammation, high ESR/CRP and/or clinically relevant extra-articular manifestations), treatment with disease-modifying drugs, such as methotrexate, sulfasalazine, leflunomide, should be considered at an early stage.
3. In patients with active psoriatic arthritis and clinically relevant psoriasis, a disease-modifying drug that also improves psoriasis, such as methotrexate, should be preferred.
4. Local injections of corticosteroids should be considered as adjunctive therapy in PsA; systemic steroids at the lowest effective dose may be used with caution.

Level
1b
1b
1b
* 1b
† 1b
† 4

Grade
A
B
A
C

Note:
* In patients with active disease (particularly those with many swollen joints, structural damage in the presence of inflammation, high ESR/CRP and/or clinically relevant extra-articular manifestations), treatment with DMARDs, such as MTX, SSZ, LFN, should be considered.
† At an early stage.
§ Local injections of corticosteroids should be considered as adjunctive therapy in psoriatic arthritis.
¶ Systemic steroids at the lowest effective dose may be used with caution.

EULAR recommendations for the management of PsA, with levels of evidence, grade of recommendations

Recommendations
5. In patients with active arthritis and an inadequate response to at least one synthetic disease-modifying antirheumatic drug, such as methotrexate, therapy with a tumour necrosis factor inhibitor should be commenced.
6. In patients with active enthesis and/or dactylitis and insufficient response to nonsteroidal anti-inflammatory drugs or local steroid injections, tumour necrosis factor inhibitors may be considered.
7. In patients with predominantly axial disease that is active and has insufficient response to non-steroidal anti-inflammatory drugs, tumour necrosis factor inhibitors should be considered.
8. Tumour necrosis factor inhibitor therapy might exceptionally be considered for a very active patient naive of disease-modifying treatment (particularly those with many swollen joints, structural damage in the presence of inflammation, and/or clinically relevant extra-articular manifestations, especially extensive skin involvement).
9. In patients who fail to respond adequately to one tumour necrosis factor inhibitor, switching to another tumour necrosis factor inhibitor agent should be considered.
10. When adjusting therapy, factors apart from disease activity, such as comorbidities and safety issues, should be taken into account.

Level
1b
1b
2b
4
2b
4

Grade
B
B
C
D
B
D
so in presence of extra-articular manifestations, DMARD treatment should be initiated immediately. This treatment should be continued for a period of 3 to 6 months, according to the physician's opinion, then an anti-TNF agent can be added to the background therapy (usually, methotrexate is the preferred treatment). Then the use of corticosteroid local injections is considered: several forms of arthritis are mono-oligoarticular and in order to improve the clinical pattern it is possible to use intralesional corticosteroids, always continuing the ongoing background therapy. Greater caution is required in case of use of systemic corticosteroids, especially if cutaneous manifestations are present for the risk of rebound effect to steroid discontinuation. The fifth point contains recommendations for patients with active arthritis not adequately responding to DMARDs. These patients should switch to anti-TNF agents, just like patients with enthesitis and dactylitis who are in the same situation. Also with regard to axial forms, it is recommended not to prolong DMARD treatment or anti-inflammatory drugs alone in case of lack of efficacy, because these patients hardly have a satisfactory response to these treatments. Recommendation number 8 refers to the first-line use of anti-TNF agents which – based on a clinical dermo-rheumatologic assessment – can be considered in all cases where the rheumatological pattern shows a poly-articular form, in presence of structural damage with high inflammation indexes, but especially when a severe and extended concomitant cutaneous involvement is present; this recommendation summarizes once again the importance of a cooperation between rheumatologists and dermatologists in the clinical practice, not only for diagnostic purposes, but also for choosing the treatment. What happens if a good therapeutic response is not obtained with an anti-TNF agent? First of all, the reasons for failure should be understood. Not always clinicians try to understand if the therapeutic failure is primary or secondary. If a patient does not respond to an anti-TNF agent from the beginning, a switch can be done, i.e. change to another anti-TNF agent and assess its efficacy. If the failure is considered to be secondary, i.e. it has occurred after a period of clinical response which was assessed to be effective, it is necessary to carefully assess patient therapeutic adherence, obviously in case of drugs administered at home; with regard to the issue of anti-TNF loss of efficacy, clinicians increasingly ask to use laboratory kits for the measurement of anti-drug antibodies in the clinical practice. This method is currently limited to use in a few territorial centers. It should be specified that within the assessment of patients with PsA, response to a treatment can be considered not only in terms of complete remission of clinical signs and symptoms but also in terms of disease activity decrease (low disease activity) if it is not possible to achieve complete and stable response. Unpublished clinical data from a study carried out at the Department of Clinical Medicine and Immunological Sciences, Rheumatology Unit of the Policlinico in Siena, in 269 patients with serum-negative spondyloarthritis – diagnosis of psoriatic arthritis and spondylitis – showed that patients received 356 therapeutic cycles of different anti-TNF agents. 98 were treated with adalimumab, 180 with etanercept and 78 with infliximab. Of the 97 patients who discontinued the treatment: 27 out of 98 in the adalimumab group (28%), 40 out of 180 in the etanercept group (22%) and 30 out of 78 in the infliximab group (39%). Etanercept showed the lower number of discontinuations. We should remember that these drugs are often associated with methotrexate for the above-mentioned reasons. Reported adverse events occurred in 11% of patients in the adalimumab group, and in 11% of patients treated with etanercept, a substantially similar percentage. The assessment of lack of efficacy or therapeutic failure (without specifying if primary or secondary failure) showed 9.4% cases for etanercept, 16% for adalimumab and 25% for infliximab; these differences were statistically significant.

In 2007, the Italian Society of Rheumatology (SIR) supported by the Italian Medicine Agency (AIFA) created a database called MonitorNet (10), with the aim of long-term monitoring of patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (SA), treated with biological agents. A recent analysis of the database, which has not been published yet, showed that the disease for which treatment with biological agents seems to be maintained for a shorter period of time is rheumatoid arthritis followed by psoriatic arthritis, while patients with ankylosing spondylitis seem to remain on treatment for the longest period. The analysis was carried out in 2,640 patients with rheumatoid arthritis and 1,220 with spondyloarthritis (PsA and SA), with a mean follow up of seventeen months. Treatment survival is longer in patients with spondyloarthritis than rheumatoid arthritis and overall etanercept and adalimumab showed a longer survival vs infliximab (Figure 9).

References


