Do Biologic-treated Psoriatic Arthritis Patients with Spondylitis Respond Differently with or without Concomitant Methotrexate from Patients without Spondylitis?

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The Journal of Rheumatology is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
Do Biologic-treated Psoriatic Arthritis Patients with Spondylitis Respond Differently with or without Concomitant Methotrexate from Patients without Spondylitis?

How effective is methotrexate (MTX) in psoriatic arthritis (PsA)? Should we use MTX in combination with biologic therapy in PsA? Does MTX increase therapeutic benefit when used in combination with biologics, either because of its own immunomodulatory effect or its ability to decrease immunogenicity to biologics? Or does MTX not provide additional benefit over and above the biologic agent? Instead, does it contribute only problems from a tolerability and safety perspective?

Despite the fact that MTX is the most commonly used immunomodulatory drug in PsA, these questions still have not been satisfactorily answered. A variety of studies sheds light on these questions, but uncertainty remains.

In this issue of *The Journal*, Behrens, et al study a large registry cohort in Germany to attempt to address a corollary question. Knowing that MTX is not effective in treating the spinal symptoms of ankylosing spondylitis, they ask the following question: In a cohort of patients with PsA, about half treated with adalimumab (ADA) monotherapy and half with concomitant MTX, if PsA subjects with spondylitis symptoms are analyzed separately from those with peripheral inflammatory musculoskeletal symptoms only, is there any difference in response to 2 years of treatment based on MTX background?

There have been few placebo-controlled trials to establish the efficacy of MTX in PsA using the low-dose MTX regimen used for the treatment of rheumatoid arthritis (RA) and psoriasis. Neither Willkens, et al nor Kingsley, et al were able to demonstrate benefit of MTX over placebo as assessed by arthritis measures used at the times of those trials, although patient global assessment and some skin measures showed modest improvement. Arguably, these were not fair trials in that the first trial studied few patients and included a low-dose arm (7.5 mg as well as 15 mg) whereas the more recent trial had significant patient dropout and included many patients with relatively low disease severity. Neither trial assessed radiographic outcomes, so ability to have an effect on structural damage was not assessed. On the other hand, an open-label study comparing MTX with MTX plus infliximab (IFX) in a relatively early PsA cohort demonstrated good American College of Rheumatology (ACR) response in the MTX monotherapy arm: ACR 20/50/70 responses of 67/40/19%, respectively. Although these results need to be taken with a grain of salt since this was an open-label study, nonetheless they give some support to the clinically observed positive responses of peripheral arthritis seen in some patients with PsA in routine clinical practice. In any case, firm evidence is lacking from a placebo-controlled trial, adequately powered and dosed in an appropriate PsA cohort, leaving us in a state of uncertainty about the effect of MTX monotherapy in PsA.

Can MTX, when used in combination with a biologic agent, provide additional benefit beyond the benefit achieved from the biologic alone? This question has been addressed in depth in the context of RA. Numerous studies have suggested that addition of MTX to biologic therapy will yield superior clinical and radiographic outcomes compared to biologic or MTX monotherapy. Thus, combination biologic plus MTX therapy has become standard practice in RA. Evidence to answer this question in PsA is lacking. In the phase III trials of various biologics, including anti-tumor necrosis factor, anti-interleukin 12 (IL-12)/IL-23, and anti-IL-17, which included biologic monotherapy and biologic combined with MTX arms, the combination of biologic with MTX did not yield greater benefit than biologic monotherapy in arthritis and skin responses. Because the patients in these trials were considered to be MTX inadequate responders, it is not appropriate to judge the potential value of MTX combination from these studies.

An indirect way to assess such value is to look at survival benefits provided by MTX plus biologic treatment compared to biologic monotherapy. This approach was applied in a recent study by Behrens, et al, who found that MTX combination therapy was associated with a significant survival benefit compared to biologic monotherapy. These findings support the notion that combination therapy may provide additional clinical benefit beyond that achieved by biologic monotherapy alone.
curves of clinical registry subjects using biologic mono-
therapy versus combination with MTX. This has been studied
in the Norwegian, Swedish, and CORRONA PsA registries
in relation to etanercept (ETN), ADA, and IFX\textsuperscript{14,15,16}. IFX
survival is more prolonged when MTX is combined
compared to IFX monotherapy. This does not appear to be
the case with ETN and is possibly not the case with ADA.
One explanation for these observations, at least partially, is
that more prolonged survival taking IFX plus MTX denotes
more sustained effectiveness, whereas ETN and possibly
ADA can have sustained effectiveness in monotherapy form.
This could be the result of a direct added benefit of MTX in
those patients, of reduced immunogenicity against IFX with
the use of MTX, or both. One expects a certain amount of
immunogenicity against IFX given its chimeric antibody
property. However, it is important to keep in mind that this
is clinical registry data, so firm conclusions cannot be drawn.

Vogelzang, et al have studied the effect of anti-drug
antibodies against ADA in PsA and demonstrated that the
presence of such antibodies was associated with lower serum
levels of ADA and with lower treatment benefit; moreover,
concomitant use of MTX could reduce anti-drug antibody
formation\textsuperscript{17,18}. These findings suggest that ADA effec-
tiveness in some patients can be increased through use of
MTX to inhibit anti-drug antibody formation. These findings
have not yet translated into being readily useful in clinical
practice, i.e., in terms of being able to easily and reliably
measure drug antibody levels.

In this issue of The Journal, Behrens, et al have attempted
to determine whether PsA patients with inflammatory spine
disease due to PsA have a different response when ADA is
combined with MTX versus patients with purely peripheral
arthritis\textsuperscript{1}. In large cohort studies, inflammatory spondylitis
involving the spine and/or sacroiliac joints is suggested to
occur in about 40% of patients with PsA\textsuperscript{19}. In PsA clinical
trials, spine involvement and spine response to treatment is
not usually assessed because patients with spondylitis are in
the minority, its presentation can be quite variable, and
accurate spondylitis diagnosis and assessment of response
would require extensive and expensive magnetic resonance
imaging (MRI), as well as clinical assessment. Thus, to
establish treatment recommendations for PsA spondylitis,
international groups such as the Group for Research and
Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)
use data from ankylosing spondylitis (AS) trials as a
surrogate for spondylitis response in PsA\textsuperscript{20}. In AS studies,
one of the traditional oral disease-modifying antirheumatic
drugs (DMARD), including MTX, have demonstrated
efficacy in the spinal manifestations of the disease. Thus, we
generally assume, although it is not proven, that similar
findings would be found in PsA spondylitis. If this is the case,
and a substantial percentage of PsA patients in a cohort have
spondylitis, then when studying whether combination MTX
and biologic is more effective than biologic alone, it is
possible that nonresponse in the spine could diminish the
ability to discriminate between patients using MTX and those
who are not.

The Behrens study was a non-interventional study
involving 355 German centers from whom 1455 patients with
PsA being treated with ADA were analyzed. Of these
patients, 20% were considered to have axial involvement, i.e.,
PsA spondylitis, and the remaining 80% constituted the
“peripheral” group. In both groups of patients, about 55%
were treated with ADA monotherapy and the remainder with
concomitant MTX.

An important limitation of the study, acknowledged by the
authors, was that determination of axial involvement was
based on the investigator’s clinical judgment — not on
objective markers such as radiography or MRI. Presumably,
the investigator determined that the patient had inflammatory
back pain — even this was not specified — or had some other
feature that allowed discrimination between inflammatory
spondylitis and degenerative or mechanical back pain (a
difficult distinction to make in the absence of objective
markers). However, it is somewhat reassuring that the preva-
lence of spondylitis was just 20% in this study, i.e., not higher
than the expected prevalence.

The key message from their study was that ADA treatment
led to significant improvement in measures of PsA other than
spondylitis, in both the spondylitis-present and spondyl-
itis-absent group, and there was no difference in the degree
of response in the MTX-present as compared to the
MTX-absent groups when multiple regression analyses were
applied to account for baseline differences between groups.
Safety and tolerability was also similar between MTX-pre-
sent and MTX-absent groups. A further analysis of patients
who changed therapy (adding or dropping MTX) during the
observation period did not show an effect of this change on
treatment response, suggesting that the lack of difference in
response was due to differential dropout. Total withdrawals
occurred in 32% of spondylitis-present and 24% of spondyl-
itis-absent patients and were the same regardless of
concomitant MTX therapy, as was the Kaplan-Meier survival
curve for ADA persistence.

Unlike the paradigm of treatment in RA, wherein the
combination of biologic agent plus MTX is considered the
optimal approach to therapy to provide further immunomod-
ulation and prevention of immunogenicity, in PsA the picture
is different. Controlled trials, albeit of insufficient strength
and quality, have failed to show clear benefit of MTX
compared to placebo. Concomitant MTX does not clearly
affect ETN or ADA persistence, but does affect IFX
 persistence in PsA clinical registries. Now the Behrens study
provides analysis of the subsets of PsA patients with and
without spondylitis treated with ADA, and here, too,
concomitant MTX does not appear to affect treatment
response, adverse effects, or persistence. On the other hand,
data from Vogelzang demonstrate that MTX can reduce ADA
anti-drug antibodies, and thus could be helpful in the subgroup of patients in whom such antibodies will affect therapeutic response — if we can figure out who that will be. So there is no clear-cut guidance; and not, as in RA, a clearly positive role for MTX in most cases.

The reader will appreciate that we may get some guidance from a study now under way. Eight hundred and forty patients with PsA who are naive to MTX are being randomized to MTX alone, ETN alone, and the combination of these 2 agents. Endpoints will include measures such as ACR response, achievement of minimal disease activity, enthesitis, dactylitis, skin and nail response, and radiographic outcomes. Such a substantial prospective trial, as well as ongoing mining of large clinical cohorts and registries, as reflected in the Behrens paper, may provide more sound guidance regarding biologic monotherapy versus combination for optimal clinical management of patients with PsA.

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