OMERACT 7 Special Interest Group

Concomitant Therapies as an Outcome Measure. Part 1: Drugs

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ABSTRACT. Concomitant therapy intake (i.e., drugs other than the study drug) could potentially be used as an outcome measure in therapeutic trials in musculoskeletal disorders. The objective of this Special Interest Group (Part 1) was to investigate this possibility. Concomitant therapy intake could be used as an outcome measure in 2 ways: either as an associated outcome measure if it was determined there was interaction between the study drug and the concomitant drug, or as an outcome measure in itself if concomitant drug intake was deemed important in its own right and fulfilled the OMERACT filter requirement. These 2 aspects were discussed in the session and then put to a vote. (J Rheumatol 2005;32:2447–8)

Key Indexing Terms:
OUTCOME MEASURES TREATMENT EFFECT INTERACTION CONCOMITANT

Definition of Concomitant Therapy

Concomitant therapy in randomized controlled trials can be defined as any therapy other than the study drug. This comprises 3 main situations:

1. Rescue therapy: A drug is given as backup in case of necessity, i.e., insufficient efficacy of the study drug; this therapy is planned initially in the protocol; for example, acetaminophen rescue in nonsteroidal antiinflammatory drugs (NSAID) in osteoarthritis (OA).
2. Concomitant therapy: Therapy that predates the study and is continued throughout, but the dosage may be modulated according to necessity; for example, corticosteroids in disease-modifying (DMARD) trials in rheumatoid arthritis, or for NSAID in trials involving biological agents in ankylosing spondylitis.
3. "Alternative" therapy: Therapy that, when instituted, results in the primary endpoint being considered as a failure could be called alternative therapy. This therapy is given only in case of inefficacy of the study drug. This is the case for total joint arthroplasty in DMARD trials in OA. Here the conventional primary outcome measure disappears, e.g., radiographic joint space width after total hip replacement. This aspect of concomitant therapies (i.e., alternative therapy) is discussed elsewhere in these proceedings in the Special Interest Group, Part 2[1].

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Concomitant Drug Therapy as a Potential Outcome Measure

Concerning concomitant drugs, several questions arise:

1. How should the information regarding concomitant therapy be collected in clinical trials?
2. Does concomitant therapy intake modify the symptomatic conventional endpoint? Could concomitant therapy intake be considered as a potential endpoint in combination with the symptomatic conventional endpoint?
3. Could concomitant therapy intake be considered as a potential endpoint in its own right?

How should the information regarding concomitant therapy be collected in clinical trials?

Often the intake of concomitant treatments is not noted in a standardized way and this renders comparisons of concomitant treatment intake between studies difficult[2]. It would be interesting to propose a standardized way of collecting data concerning concomitant therapies in trials (e.g., How to determine the equivalence of 120 days during which analgesics are taken in one trial versus 120 tablets of analgesics in another trial?).

There are several ways investigators can collect information regarding concomitant therapy intake in clinical trials: (1) dedicate a page of the research file (CRF) for the recording of any concomitant therapy; (2) provide rescue therapy

and perform a pill count either at the end of the study or at each consultation; (3) provide a diary for patients to note the number of pills taken and the dates taken; (4) require completion of a specific questionnaire at each visit (e.g., "Since the last visit, how many days a week did you require analgesics?"). Finally. there are 2 possible results that can then be entered into the database: the number of days with at least one intake (days with/without concomitant therapy intake), and the number of tablets.

Based on data obtained from several databases concerning short term placebo-controlled NSAID trials in OA (6 to 12 wks), it was seen that (1) patient diary and data collected on the CRF page were not adequate (too many missing data); (2) pill count is easy to perform but necessitates rescue therapy to be provided; (3) if rescue therapy is not provided it is highly recommended to ensure specific collection of this data in the CRF, by asking a specific question related to either the number of tablets or the number of days of concomitant therapy intake.

Does concomitant therapy intake modify the symptomatic conventional endpoint? Could concomitant therapy intake be considered as a potential endpoint in combination with the symptomatic conventional endpoint?

For example, in a study of NSAID in OA, where the conventional endpoint is pain, acetaminophen intake (the allowed rescue therapy) may modify the conventional endpoint, such as pain, functional impairment, or global assessment. Concomitant drug therapy intake should perhaps enter into the analyses, because in some cases the discriminant capacity might be better when taking into account concomitant therapy intake. For example, NSAID intake coupled with Assessments in Ankylosing Spondylitis Working Group 20% criteria[3] (ASAS 20) could be more discriminant than ASAS 20 criteria alone in ankylosing spondylitis trials; corticosteroid intake could be coupled with American College of Rheumatology 20% response (ACR 20) or ACR 50 criteria in rheumatoid arthritis trials; analgesic intake could be coupled with OARSI/OMERACT[4] responder criteria in OA NSAID trials. In order to investigate this hypothesis, the example of acetaminophen intake in short-term placebo-controlled NSAID trials in OA was used, with pain, functional impairment, and patient global assessment as main symptomatic outcome measures.

Based on the results (data not shown), it seems that (1) the discriminant capacity of the conventional outcome measures is not increased when rescue therapy is taken into account; (2) the discriminant capacity of the conventional outcome measures is higher in the subgroup of patients requiring rescue therapy.

Could concomitant therapy intake be considered as a potential endpoint in its own right?

For this purpose concomitant therapy intake would have to fulfill the OMERACT filter, i.e., for truth, discrimination, and feasibility[5]. In order to investigate this hypothesis, the same databases were used. Based on the results (data not shown), it seems that concomitant therapy (acetaminophen intake in NSAID OA trials) fulfills the OMERACT filter, i.e., for truth: it reflects severity in OA; reliability: intake is stable across the study period for a given patient; and discriminant capacity is correct. Based on this data-driven approach it was voted by OMERACT participants that concomitant drug therapy could be used as a secondary outcome measure in its own right.

Conclusion

The Special Interest Group (Part 1) on concomitant drug therapy as an outcome measure raised the following points:

- The need for standardized terms regarding concomitant therapies (e.g., rescue vs concomitant vs alternative therapy);
- Recommendations regarding collection of information related to concomitant therapy intake; and
- The proposal of a research agenda to further evaluate concomitant therapy intake as a potential outcome measure either in its own right or in combination with conventional outcome measures.

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