
Methotrexate – the anchor drug – an introduction

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Conflict of interest: Dr Pincus serves as a consultant to Bristol-Myers Squibb, Inc., Genentech, and UCB Pharma, and receives research support from Bristol-Myers Squibb, Inc.

Dr. Cronstein holds or has filed applications for patents on the use of adenosine A_{2A} receptor agonists to promote wound healing and use of A_{2A} receptor antagonists to inhibit fibrosis; use of adenosine A₁ receptor antagonists to treat osteoporosis and other diseases of bone; the use of adenosine A₁ and A_{2B} receptor antagonists to treat fatty liver, and; the use of adenosine A_{2A} receptor agonists to prevent prosthesis loosening. He has been a consultant (within the past two years and all <\$10,000) for King Pharmaceutical (licensee of patents on wound healing and fibrosis above), CanFite Biopharmaceuticals, Savient Pharmaceuticals, Bristol-Myers Squibb, Roche Pharmaceuticals, Cellzome, Tap (Takeda) Pharmaceuticals, Prometheus Laboratories, Regeneron (Westat, DSMB), Sepracor, Amgen, Endocyte, Protalex, Allos, Inc., Combinatorx, Kyowa Hakka; has received honoraria from Tap (Takeda) Pharmaceuticals; and has been received for membership in the Scientific Advisory Board of CanFite Biopharmaceuticals. Dr Braun has declared no competing interests.

The 12th annual Supplement of *Clinical and Experimental Rheumatology* concerning Contemporary Topics in Rheumatic Diseases is entitled “Methotrexate in Rheumatic Diseases.” Over the last three decades, methotrexate has become the “anchor drug” for rheumatoid arthritis (RA) (1, 2), taken by far more patients than any other medication (3). Methotrexate also is widely used at this time in treatment of all inflammatory rheumatic diseases. The Supplement addresses pharmacologic properties, mechanisms of action, use in different diseases, and combinations with other DMARDs and biological agents associated with methotrexate.

This compendium continues a tradition of compiling topical articles by leading experts as a scholarly endeavour in which articles are written entirely by the listed authors, without any participation of “writing companies” or “ghost writers,” etc. The articles present not only comprehensive summaries of the medical literature and statistical data, but also incorporate invaluable interpretation based on the authors’ own direct research and clinical experience. This approach may provide more accurate information to guide clinical care than many reports of “hotel-based medicine” (4), written without such experience.

A volume concerning methotrexate is particularly timely, as most medical literature and educational programs for rheumatologists over the last decade have been directed to biological agents. However, methotrexate is taken by many more patients (3), including most patients who take biological agents or who are enrolled in therapeutic trials with newer small molecules. A significant knowledge void remains among many physicians and other health professionals, as well as patients, regarding accurate information concerning methotrexate in rheumatic diseases:

1) Methotrexate continues to be regarded in much of the general medical community as similar to other

disease-modifying anti-rheumatic drugs (DMARDs) such as sulfasalazine and leflunomide in efficacy for rheumatoid arthritis (RA) and adverse events, based on systematic reviews and meta-analyses of clinical trials (5). However, methotrexate is considerably more likely to be taken by patients in rheumatologic care for RA than these other agents (3). Furthermore, courses of methotrexate are considerably more likely to be continued over 5 years than courses of other DMARDs (or biologic agents) (6), reflecting greater effectiveness and tolerability and fewer adverse events.

2) The efficacy of methotrexate is similar to that of biologic agents in initial treatment of patients with RA, although 20–40% of patients may require an addition of biologic agents, which, when used with methotrexate, are clearly superior to methotrexate alone in patients who had experienced a prior incomplete response to methotrexate.

3) Methotrexate retards radiographic progression in most patients (7), although again 20–40% of patients may have greater retardation upon addition of a biologic agent (8). Nonetheless, differences in radiographic progression seen in patients who take methotrexate or a biologic agent are very small, and may be of limited clinical importance although statistically significant.

4) The dosage of methotrexate that is now recommended is between 15–30 mg/week, and parenteral administration appears to increase bioavailability and efficacy with some increase in adverse events. Nonetheless, many patients experience adequate responses to lower doses, and even doses of 2.5–7.5 mg/week in the few patients who do not tolerate higher doses appear to improve patient status.

5) Methotrexate is administered to

patients with rheumatic diseases in doses 10–100-fold lower than those used to treat patients with malignancies. Nonetheless, adverse events and drug interactions associated with low-dose methotrexate in dosages used in patients with rheumatic diseases often are noted incorrectly to be identical in frequency and severity to those observed in patients receiving high-dose methotrexate for the treatment of neoplastic diseases in some medical textbooks (6), online drug resources, and information provided to patients when filling a prescription.

6) In the treatment of rheumatic diseases, methotrexate appears to act primarily through a mechanism to reduce inflammation (9), rather than through the cytotoxic mechanism seen for high-dose methotrexate. Therefore, blood cell counts need not be reduced to achieve short-term efficacy and long-term effectiveness, and folic acid supplements can be used to reduce toxicity.

7) Methotrexate can be given with considerable safety as an “n-of-1 trial” in early arthritis (10), even when the diagnosis remains uncertain, with a defined endpoint of 3 to 6 months. It is possible that weekly low-dose methotrexate may well have a risk: reward ratio as favourable as most antibiotics prescribed over the telephone by physicians who express great reservations about treating

patients with weekly low-dose methotrexate.

8) Methotrexate is now used in many inflammatory rheumatic conditions – in most cases with moderate success. A primary problem, however, is the absence of data from clinical trials and observations from standard care in these conditions. Unfortunately, there may never be enough patients or resources for clinical trials in all diseases. Clinical observations can be quite informative – that’s how methotrexate was established initially for RA (11).

Taken together, over the last decades, methotrexate has become the most important conventional drug treatment in rheumatology, especially for patients with RA, but also for other (though not all other) inflammatory rheumatic diseases.

More accurate interpretation of information for physicians and other health professionals, as well as patients, concerning use of weekly low-dose methotrexate in contemporary care for rheumatic diseases could improve care and outcomes for patients with RA and other rheumatic diseases.

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