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OPINION ARTICLE

Methotrexate in Psoriasis: Do We Need to Give a Test Dose?☆

Metotrexato en psoriasis: ¿es necesaria una dosis de prueba?

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After more than 50 years' experience with methotrexate and despite the lack of appropriate trials, the efficacy of this drug for treating psoriasis is unquestioned. However, the numerous guidelines and reviews on the use of methotrexate¹⁻¹² have not erased practitioners' uneasiness about unforeseen potential side effects, resulting in considerable variation in the prescribing practices among physicians. One difference in practice is the use or not of a so-called 'test dose' (a lower initial dose given to assess the likelihood of an unexpected acute adverse event).

Aminopterin was first used empirically for psoriasis and rheumatoid arthritis in 1951 by Gubner, an internist, and coworkers,¹³ and in 1958 this drug was specifically mentioned as a treatment for psoriasis.¹⁴ In 1972, the US Food and Drug Administration approved methotrexate for this indication. Dermatologists promptly began to assess the use of both aminopterin and methotrexate in this disease, testing twice weekly parenteral doses of 50–75 mg,¹⁵ very small daily doses for several consecutive days a month (0.5–0.6 mg every 4–6 h for 10 d/mo),¹⁶ and topical application for psoriatic plaques.¹⁷ After this initial stage, in 1969 the usefulness of a weekly dose was established,¹⁸ and in 1971, the possibility of dividing the weekly dose into 3 doses administered at 12-h intervals (Weinstein's regimen) was suggested.¹⁹ These prescription practices were an attempt to base dosing on the pharmacokinetics of methotrexate,²⁰ on studies of cell kinetics,²¹ and on the unproven assumption that adverse gastrointestinal events would thereby be prevented or attenuated. Although minimum and maximum doses have not been universally established, the weekly administration

of 7.5–25 mg is recommended as an effective therapeutic range in psoriasis.¹²

The toxicity of methotrexate depends on the extracellular concentration of the drug and the period of exposure; toxicity for a given dose will therefore be proportional to the period of exposure to it. In theory, a toxic event can be anticipated by measuring blood levels of the drug (levels higher than 0.01 μmol/L after intramuscular injection of 10 mg should lead to suspicion of toxicity)²²; however, we do not measure concentrations routinely.

Most adverse reactions related to low-dose methotrexate (gastrointestinal and mucocutaneous) are mild, appear in the first 24–48 h after administration, and do not usually require interruption of the treatment. In some cases reactions can be attenuated by regulating or dividing the dose, by administering the drug intravenously at night, or by having the patient take folic acid supplements.²³ Gastrointestinal toxicity presents in 60% of patients as stomatitis, nausea, vomiting, indigestion, abdominal pain, dyspepsia, diarrhea, anorexia, and weight loss.²³ Aphthous stomatitis is associated with higher doses of methotrexate but folate supplements improve tolerance of the course of treatment.²⁴ The most severe toxicity associated with methotrexate is specific to certain organs and tissues, affecting the blood, liver, and lung; related mortality rates decrease in that order.²⁵ The development of toxicity is often associated with concomitant factors, accumulation of drugs or overdose, which are not fully understood.⁶ These factors must be remembered when selecting patients for treatment with methotrexate.

However, a similar profile of adverse effects can also be seen with other drugs for which we do not consider test doses. For most dermatologists the test dose was handed down to us as clinical practice when we were residents, and we accepted it uncritically, presumably because it was a matter of prudence in the prescription of medication and

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out of respect for our superiors; that was the case for me and I believe my experience was typical. Why then do we not start with test doses of cyclosporin, nonsteroidal anti-inflammatory drugs (which, incidentally, cause more frequent adverse effects), tetracyclines, or any other drug we use routinely? Is it perhaps because hypersensitivity reactions to methotrexate, but not to cyclosporin, began to be reported at a certain historical moment? The initial trials and reports based on large patient series do not mention hypersensitivity reactions but rather toxicity associated with high doses and/or renal failure, and, in most cases, transitory transaminase elevation not requiring suspension of treatment.^{1,15,16,18,26} The test dose nonetheless continues to be recommended in most published guidelines, although I have found no documented account of its utility or trial evidence supporting it.

In my opinion, none of the toxicities associated with methotrexate can be considered hypersensitivity reactions, except for methotrexate-associated pneumonitis, which normally appears several weeks after treatment begins (nearly always after the full dose is reached). The test dose can therefore not be used as an excuse for preventing this serious, though unusual, toxic event. From a theoretical standpoint, assessing a test dose is more relevant in cases where methotrexate is being reintroduced, as allergic hypersensitivity could be expected then rather than at the start of treatment. Interestingly, the general assumption on reintroducing the drug is that the previous experience is sufficient indication of safety and no test dose is needed. However, the literature offers mainly reports of anaphylactoid reactions after high doses in patients who had previously been exposed to methotrexate.

Acute hypersensitivity reactions—though we have no accurate catalog of exactly what to look for, whether anaphylaxis, urticaria, toxic hepatitis, bone marrow aplasia, or toxic epidermal necrolysis—have been sporadically described in the literature almost exclusively in oncology or rheumatology patients who are taking concomitant medications and high doses of parenteral methotrexate; the vast majority of these patients had been previously exposed to the drug.^{27–30} Very few cases of these reactions have been described after the initial dose and this is also true for patients with a severe underlying disease other than psoriasis and who are taking other medications. (We do note, however, a report of mild, transient purpura after a test dose of 7.5 mg³¹.) The available evidence therefore suggests that hypersensitivity reactions have mostly been described in patients who have previously taken high doses of methotrexate and have oncologic and/or rheumatologic disorders. This is not the situation for our patients taking low doses of methotrexate for psoriasis, however. Similarly, leukopenia or pancytopenia are reactions that have been described mainly in patients with underlying conditions (especially those with associated renal failure and in hemodialysis) or in cases of overdose.

What then is the purpose of a test dose? Solely for the sake of argument, we note that a test dose is indicated for the prevention of a possible non-dose-dependent hypersensitivity reaction, which might be severe and which could be watched for; or we might attenuate a reaction's seriousness by administering a small dose. Next, my understanding is that we must abandon claiming that the prevention of

possible adverse events related to drug accumulation is a criterion for deciding to use a test dose, given that a test occurs at the start of treatment. A survey of the Spanish Psoriasis Group of the Spanish Academy of Dermatology (AEDV), carried out when the association's guidelines on methotrexate use in psoriasis¹² were being drafted, included a question about the respondents' experience with test dosing. The answers we received were extremely varied: some respondents did not use one while others did—expressing fear of bone marrow aplasia, acute hepatitis, acute urticarial reaction—or “just in case of any unexpected reaction.” None of the respondents had ever witnessed such a reaction among their patients, however.

The only unexpected reaction to methotrexate in psoriasis I have seen was plaque erosion after the first few doses of the drug (hypersensitivity?). This reaction is certainly not serious and is only remarkable because of the need to recognize it as what it really is in order to avoid interpreting it as a lack of response to methotrexate and then try raising the dose, thereby leading to acute toxicity due to overdose (a practice error, as a higher dose would not be indicated).

What constitutes a test dose? That there is also variation in what practitioners consider to be a test dose was also evident in the survey mentioned above, in which respondents chose 2.5 mg, 5 mg, 7.5 mg, and 10 mg for such doses. Several guidelines suggest a test dose of 5–10 mg, or a lower one of 2.5 mg in a ‘susceptible patient’.^{10,11} The prescribing information for oral and injectable forms of methotrexate recommends an initial dose of 7.5 mg and 10 mg,³² respectively, without explicitly defining it as a test dose.

Still, doses of 7.5 mg and higher are already within the therapeutic range (7.5–25 mg/wk) for psoriasis. Is 7.5 mg the test dose when wanting to prescribe 15 or 20 mg? And what if I want to administer a 7.5-mg dose directly? What is, in principle, the dose I eventually want to reach? No studies give guidance on a theoretically optimal dose, and methotrexate is not prescribed according to weight. The precautionary measure of administering low doses would be more valid for patients with underlying risks (due to comorbidity, age, or concomitant medication).

A lower initial dose must not be confused with a test dose. The intention in the first instance is to discover the minimum effective dose rather than to prevent toxic reactions: the minimum effective dose and the test dose are not one and the same. The purpose of the test dose is to prevent an immediate acute adverse reaction that could be severe. If the reaction is idiosyncratic or the result of hypersensitivity, I believe it will matter little whether the dose is of 2.5 mg, 5 mg, 7.5 mg, or 15 mg, since the problem stems from an individual's genetic makeup and metabolism of a drug and on the molecular structure of the drug itself. Moreover, any of these doses is far lower than those that had been administered in the reported cases of hypersensitivity reactions. If the intention of a test is to prevent dose-dependent toxicity, then indeed, establishing the minimum effective dose could be considered. How can we be sure that a single dose of 2.5 mg will be safe and that a reaction will not develop after the second, third, or ninth dose? Rather than accepting the test dose as a routine practice, it would be more reasonable to maintain a low dose divided into several weekly intakes and to speak of a test or induction phase rather than a test dose.

Personally, I do not prescribe test doses, instead starting patients on an initial dose of 15 mg if they have no comorbidities associated with increased risk when taking this drug.¹² I have observed no severe acute toxicity from this initial dose³³ and consider it the optimal one for predicting the efficacy that can be expected from continuing treatment. This dose has been suggested on the basis of findings from trials that compared biologic agents to methotrexate, according to Dr Kristian Reich, speaking at the 2010 annual congress of the European Academy of Dermatology and Venereology in Gothenburg, Sweden.³⁴

In my opinion the main issue in the management of methotrexate therapy is not about dosing regimens; rather, we should be concerned with evaluating patients before starting treatment and following them closely (including monitoring laboratory test results), as we have recommended.¹² Early reviews of the use of aminopterin and methotrexate in psoriasis indicated that the possible adverse reactions encountered were related to renal or hepatic failure and rarely to hypersensitivity.^{35,36} When the use of methotrexate is considered, contraindications and special precautions for this drug must be carefully assessed. Any previous relative contraindication experienced by the patient will certainly influence the choice of dose, follow-up, and safety regimens.¹² However, this presupposes a standardized management of methotrexate similar to that of other antipsoriatic drugs, with no resort to a test dose based on uneasiness which neither experience nor evidence justifies.

Perhaps the reason for ongoing debate lies in the lack of randomized clinical trials. Methotrexate is an old drug that appeared in another era. The lack of appropriate clinical trials was denounced decades ago,³⁷ yet trials have not been widely or systematically performed for this drug as they have been for cyclosporin and biologic agents, drugs for which a test dose has not been suggested even though their potential to cause very serious adverse events is acknowledged.

Methotrexate has been the target of myths and groundless fears (high risk of pulmonary and hepatic toxicity, mutagenic potential, etc.), which have gradually faded or diminished after decades of experience.³⁸ In any case, discussions about the initial dose are not as important as the need for prompt patient evaluation and later clinical vigilance once methotrexate has been prescribed, irrespective of the initial dose.

In summary, I believe that when prescribing methotrexate in psoriasis we should consider therapeutic range; patient selection; the so-called attack, or loading, dose as well as the maintenance dose; and follow-up. A test dose, on the other hand, should not be used for fear of the unknown or figments of our imagination. Methotrexate should receive the same medical, pharmacologic, and pharmacovigilance treatment as any other drug and not be subjected to a verdict of guilty without trial.

Conflicts of Interest

The author declares that he has no conflicts of interest with regard to this opinion article. However, he has received fees for speaking at conferences, conducting clinical trials, or otherwise serving as a consultant from the following

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