Immunosuppressive Drugs in Multiple Sclerosis

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Summary

- Multiplesclerosis(MS)is considered anautoimmune disease associated with immune activity against central nervous system antigens
- Immunosuppression and immuno-modulation are themainstays of the therapeutic strategies for this disease: reduce frequency of relapses that are thought to be a result of local inflammation and consequent loss of the myelin sheath that normally surrounds axons in the central nervous system

- Immunosuppression

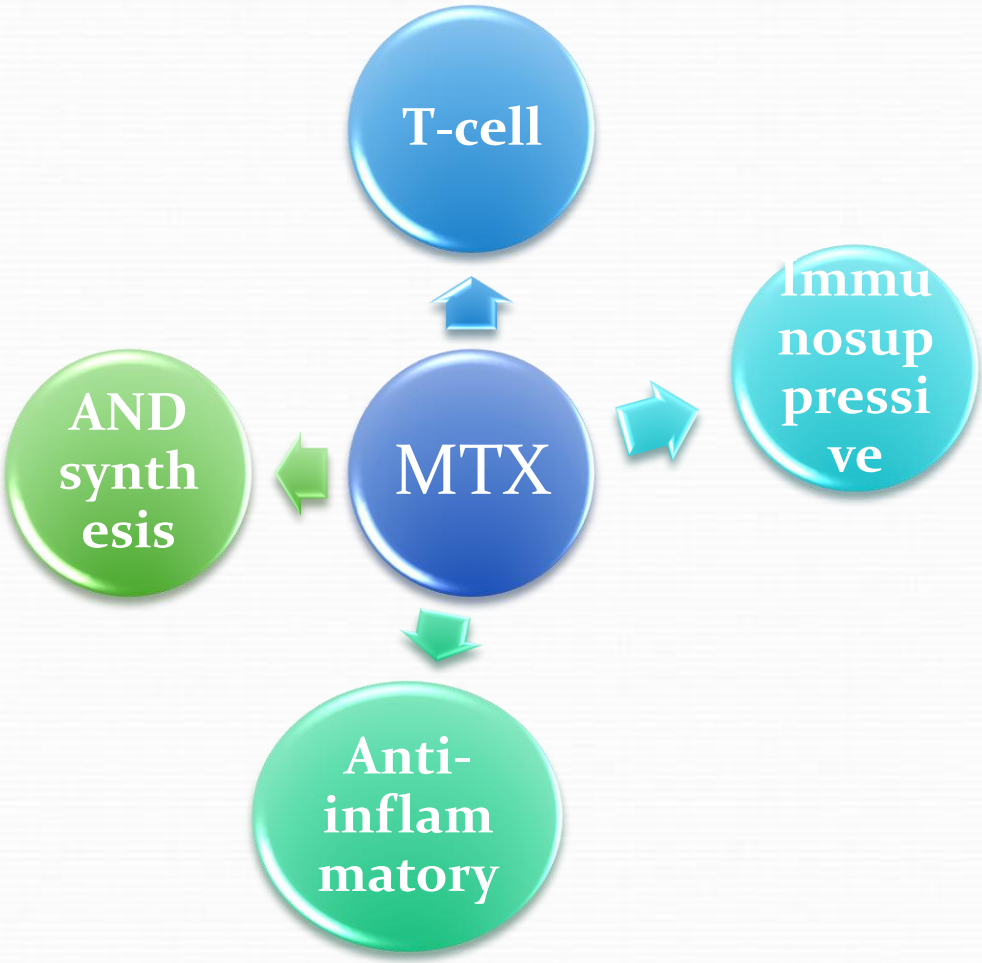
1. Methotrexate
2. Azathioprine
3. Cyclophosphamide

- Immuno-modulation

1. Methotrexate

- Methotrexate is a potent immunosuppressant, whose mode of action is predominantly through its inhibition of dihydrofolate reductase (Calabresi 1990)
- Longterm methotrexate administration is associated with serious side-effects including **hepatic fibrosis** (Colsky 1955).
- It is important to establish the efficacy of methotrexate, to ensure that people with MS are not subject to longterm exposure with a potentially toxic drug without good evidence of efficacy.

1. Methotrexate



Oral Gray,Methotrexate for multiple sclerosis,2004

Search methods

We searched the Cochrane MS Group Specialised Register (September 2007), the Cochrane Central Register of Controlled Trials (The Cochrane Library 2007, Issue 3), MEDLINE (1966 to September 2007), EMBASE (1974 to Septermber 2007), Science Citation Index (SCISEARCH), British Medical Journal Register of unpublished clinical trials and reference lists from identified trials. We also contacted manufacturers and researchers in the field.

Selection criteria

Randomised controlled trials of methotrexate for the prevention of relapses and disease progression in MS.

Data collection and analysis

We obtained 1118 citations from our literature search, but found only 2 eligible randomised controlled clinical trials. One study was excluded on the basis of inadequate allocation concealment, leaving one eligible study.

Main results

The included trial involved 60 participants with chronic progressive multiple sclerosis. There were no participants with relapsing-remitting disease. The trial showed a non-significant reduction in sustained EDSS progression and number of relapses in favour of methotrexate therapy. There was no difference in time to first relapse and no data on relapse rate. Minor side-effects were reported frequently in both methotrexate (87.1%) and placebo groups (89.7%), but there were no major side-effects.

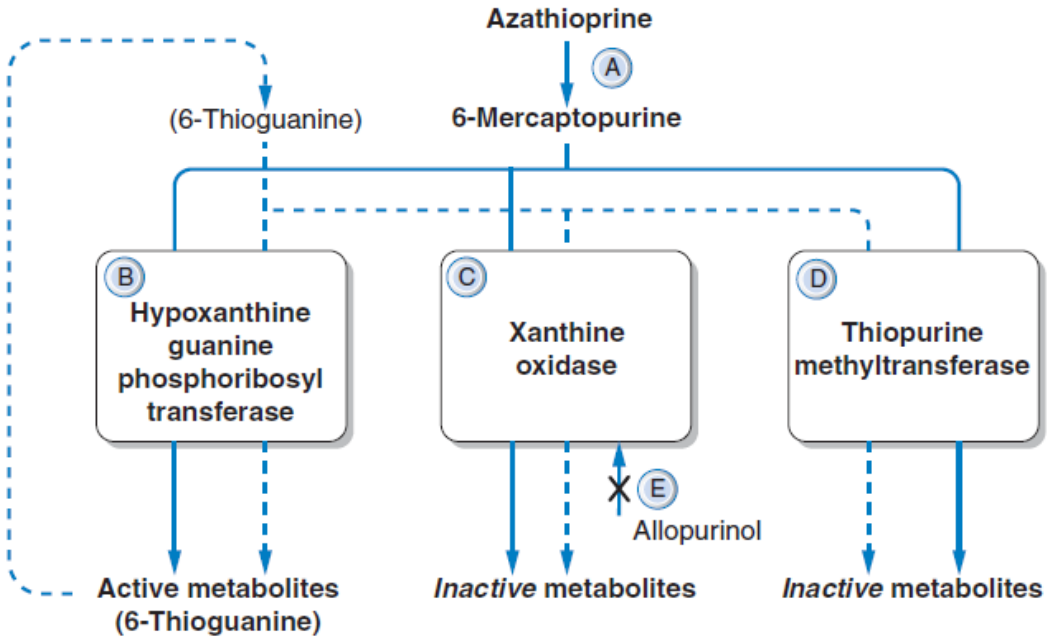
Authors' conclusions

In progressive MS, the single included trial reveals a non-significant trend in reduction of sustained EDSS progression and number of relapses in favour of methotrexate. There are no studies of methotrexate in relapsing remitting MS. Before drawing further conclusions regarding the efficacy of methotrexate in MS, further trials of people with relapsing-remitting MS or progressive MS are required.

2.Azathioprine

- is a purine antagonist -> affects DNA replication and the immune system in a number of ways.
- It impairs T-cell lymphocyte function and is more selective for T lymphocytes than for B lymphocytes (Patel 2006). A recent study further elucidates the efficacy of azathioprine in chronic inflammatory and autoimmune disease

2.Azathioprine



A **Azathioprine** is initially converted to active form **6-mercaptopurine** (6-MP).
B Hypoxanthine guanine phosphoribosyl transferase (HGPRT) converts 6-MP to active metabolites (**6-thioguanine**).
C Xanthine oxidase converts 6-MP to *inactive* metabolites.
D TPMT converts 6-MP to *inactive* metabolites; with genetic TPMT deficiency, shunting 6-MP to the HGPRT pathway occurs, with ↑↑ 6-thioguanine metabolites and subsequent *toxicity*; with genetically high TPMT levels, the result is ↓ 6-thioguanine metabolites, with *loss* of *efficacy*.
E **Allopurinol** inhibits xanthine oxidase, shunting 6-MP to HGPRT pathway, with ↑ toxicity.

- Neurologists have been using azathioprine to treat patients with MS for more than 30 years.
- Although newer immunomodulating drugs, the continuing high costs of these medications and their uncertain effects on disability progression have precluded the abandonment of azathioprine.
- A review of seven clinical studies evaluating the effect of azathioprine on MS up to 1989 concluded it was efficacious in **preventing relapses** at one, two and three years and had a slight, borderline benefit also on **prevention of disability progression** at two and three yeas (Yudkin 1991)

- The few trials that assessed disability progression with azathioprine found similar reductions to the interferon trials (Sudlow 2003).
- cost saving to the National Health Service, and produced moderate quality of life gains (McCabe 2003)
- A recent study has suggested that azathioprine seems to be effective both on clinical and imaging outcomes (Massacesi 2005). Azathioprine is approved and largely used in Europe for MS treatment (Hommes 2004)

Ilaria Casetta,Azathioprine for multiple sclerosis,2007

adverse effects.

Selection criteria

All parallel group randomised controlled trials (RCTs) comparing azathioprine treatment of a least one year duration with placebo for patients with MS. Cohorts, case controls, case series and case reports were also used to assess adverse effects.

Data collection and analysis

Potentially relevant references were evaluated and all data extracted by two independent authors.

Main results

The five trials that met our criteria included 698 patients: data from 499 (71.5%) were available for analysis of relapse frequency at one year's, from 488 (70%) at two years' and from 415 (59.5%) at three years' follow-up. Azathioprine reduced the number of patients who had relapses during the first year of treatment (relative risk reduction [RRR] =20%; 95% CI = 5% to 33%), at two years' (RRR =23%; 95% CI = 12% to 33%) and three years' (RRR =18%; 95% CI = 7% to 27%) follow-up. These results were consistent in sensitivity analysis. There was no heterogeneity among the studies.

Data from only three small trials with a total of 87 patients were available to calculate the number of patients who progressed during the first two to three years. There was a statistically significant benefit (RRR = 42%; 95% CI = 7% to 64%) of azathioprine therapy at three years' follow-up; this result was robust after sensitivity analyses and there was no heterogeneity among the trials.

Gastrointestinal disturbances, bone marrow suppression and hepatic toxicity were greater in the azathioprine group rather than in the placebo group; they were anticipated, and, by monitoring and dosage adjustment, were easily managed. Withdrawals due to adverse effects were few, occurring mostly during the first year of azathioprine treatment and mainly due to gastrointestinal intolerance (5%).

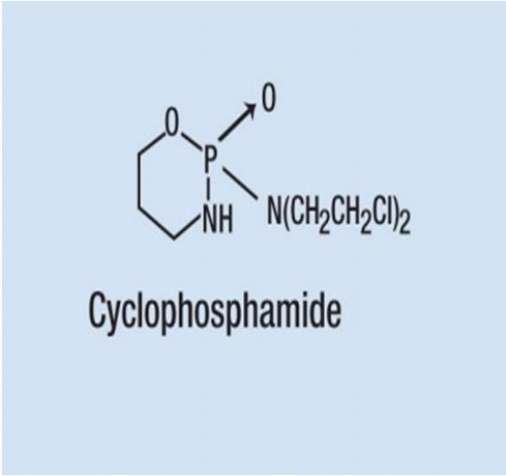
Data from the trials and from cohort and case controls studies available in the literature did not show an increase in risk of malignancy from azathioprine. A possible long-term risk of cancer from azathioprine may be related to a treatment duration above ten years and cumulative doses above 600 g.

Authors' conclusions

Azathioprine is an appropriate maintenance treatment for patients with MS who frequently relapse and require steroids. Cumulative doses of 600 g should not be exceeded in relation to a possible increased risk of malignancy. Considering the trade off between the benefits and harms, azathioprine is a fair alternative to interferon beta for treating MS. A logical next step for future trials would seem the direct comparison of azathioprine and interferon beta. In fact the direct comparison between these two widely used treatments in MS has not been made.

3. Cyclophosphamide (CFX):

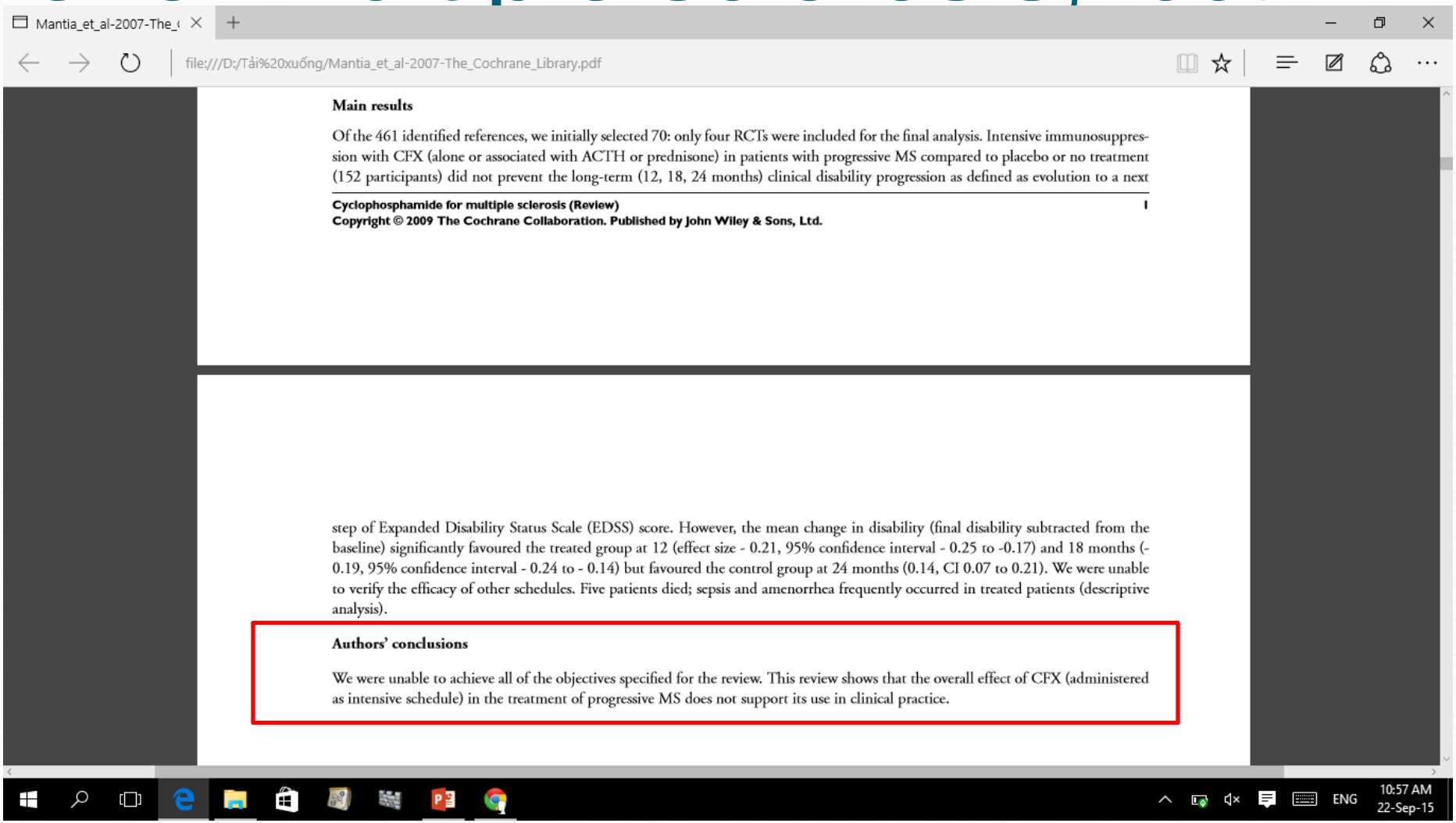
- An alkylant agent with cytotoxic and immunosuppressive effects (Calabresi 1991)
- Used in the treatment of different malignancies as well as autoimmune diseases (Wegener's granulomatosis, Periarteritis nodosa, Lupus Erythematosus Systemic)



Cyclophosphamide

- The efficacy of CFX in patients with progressive or relapsing form of MS remains controversial (Schluep 1997, Weiner 2002): Different treatment schedules : varying dosages, route of administration (i.e. oral, intravenous), duration (ranging from a few days to months) and association with other drugs (i.e. adrenocorticotropic hormone-ACTH-steroids or other immunosuppressive agents) or with plasma exchange, followed or not by pulse maintenance treatment

LaMantiaL,Cyclophosphamide for multiple sclerosis,2007



Main results

Of the 461 identified references, we initially selected 70: only four RCTs were included for the final analysis. Intensive immunosuppression with CFX (alone or associated with ACTH or prednisone) in patients with progressive MS compared to placebo or no treatment (152 participants) did not prevent the long-term (12, 18, 24 months) clinical disability progression as defined as evolution to a next

step of Expanded Disability Status Scale (EDSS) score. However, the mean change in disability (final disability subtracted from the baseline) significantly favoured the treated group at 12 (effect size - 0.21, 95% confidence interval - 0.25 to -0.17) and 18 months (-0.19, 95% confidence interval - 0.24 to - 0.14) but favoured the control group at 24 months (0.14, CI 0.07 to 0.21). We were unable to verify the efficacy of other schedules. Five patients died; sepsis and amenorrhea frequently occurred in treated patients (descriptive analysis).

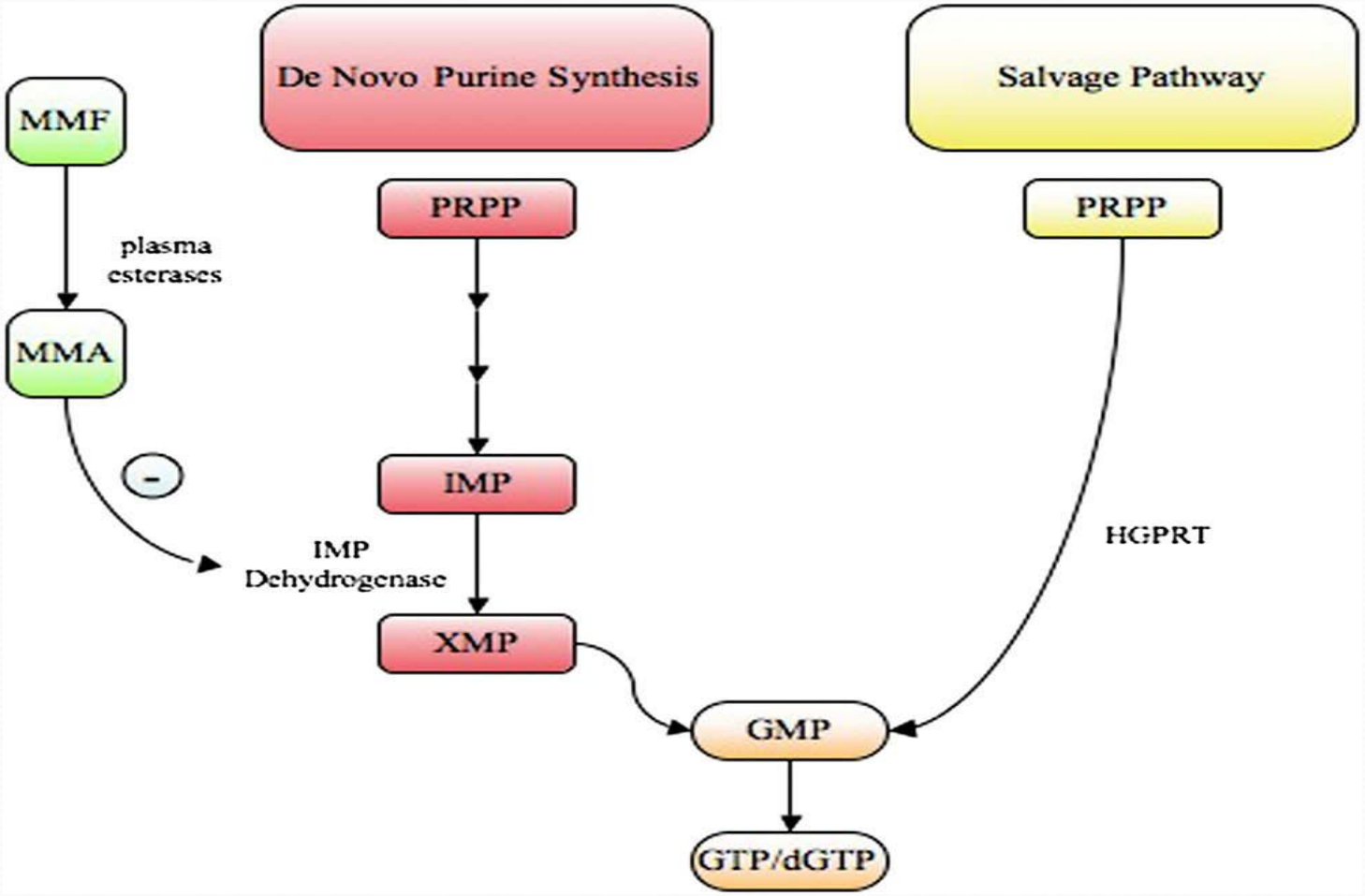
Authors' conclusions

We were unable to achieve all of the objectives specified for the review. This review shows that the overall effect of CFX (administered as intensive schedule) in the treatment of progressive MS does not support its use in clinical practice.

4. Mycophenolate Mofetil (MMF)

- MMF is an expensive immunosuppressive agent that has been used in the past few years for the prevention of allograft rejection after renal, cardiac, or liver transplant (Villarroel 2009).
- It is increasingly used in the treatment of autoimmune diseases such as MS (Etemadifar 2011; Frohman 2010; Remington 2010; Vermersch 2007)
- MMF is well tolerated; the most frequently reported adverse effects have been gastrointestinal (abdominal pain, vomiting, diarrhea) or related to the hematopoietic system

4. Mycophenolate Mofetil



Mycophenolate mofetil for relapsing-remitting multiple sclerosis

Search methods

We searched the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group Specialised Register (January 14, 2013). We searched three Chinese databases (January 2013) and checked reference lists of identified trials. We contacted authors and pharmaceutical companies to ask for additional information. We applied no language restrictions.

Selection criteria

We included randomized controlled trials with a follow-up of at least 12 months that compared MMF as monotherapy or in combination with other treatments versus placebo, another drug, or the same cointervention as the treated group.

Data collection and analysis

Two review authors independently selected the trials for inclusion, assessed trial quality, and extracted data.

Main results

One included study involving 26 participants with new-onset RRMS investigated the efficacy and safety of MMF (13 participants) versus placebo in interferon β-1a–treated participants. It was assessed to be at high risk of bias, and had a small numbers of participants receiving treatment with short-term duration. There was inadequate information provided by the study to determine the effect of MMF in reducing relapses, preventing disability progression, or developing new T2- or new gadolinium (Gd)-enhanced lesions on magnetic resonance imaging (MRI) after a 12-month follow-up period. No data were available at 24 months. No serious adverse effects were reported. All participants in the MMF-treated group suffered from gastrointestinal upset, but none of them discontinued therapy as a result.

Authors' conclusions

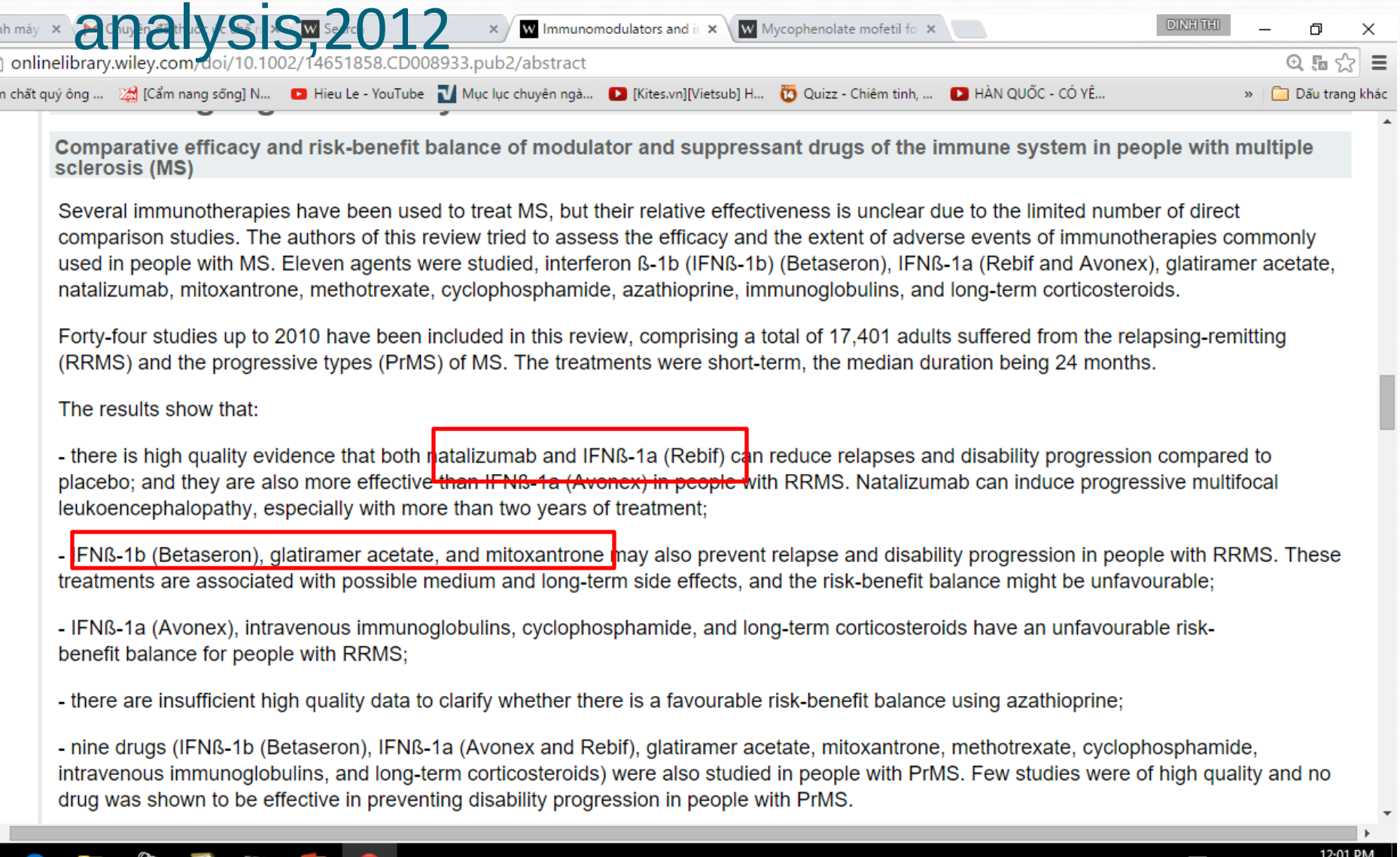
The evidence we found from one small study was insufficient to determine the effects of MMF as an add-on therapy for interferon β-1a in new-onset RRMS participants.

Consumption

- Azathioprine was efficacious in **preventing relapses and prevention of disability progression**
- MMF is well tolerated

Immunomodulators and immunosuppressants for multiple sclerosis

Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis,2012



Comparative efficacy and risk-benefit balance of modulator and suppressant drugs of the immune system in people with multiple sclerosis (MS)

Several immunotherapies have been used to treat MS, but their relative effectiveness is unclear due to the limited number of direct comparison studies. The authors of this review tried to assess the efficacy and the extent of adverse events of immunotherapies commonly used in people with MS. Eleven agents were studied, interferon ß-1b (IFNß-1b) (Betaseron), IFNß-1a (Rebif and Avonex), glatiramer acetate, natalizumab, mitoxantrone, methotrexate, cyclophosphamide, azathioprine, immunoglobulins, and long-term corticosteroids.

Forty-four studies up to 2010 have been included in this review, comprising a total of 17,401 adults suffered from the relapsing-remitting (RRMS) and the progressive types (PrMS) of MS. The treatments were short-term, the median duration being 24 months.

The results show that:

- there is high quality evidence that both natalizumab and IFNß-1a (Rebif) can reduce relapses and disability progression compared to placebo; and they are also more effective than IFNß-1a (Avonex) in people with RRMS. Natalizumab can induce progressive multifocal leukoencephalopathy, especially with more than two years of treatment;

- FNß-1b (Betaseron), glatiramer acetate, and mitoxantrone may also prevent relapse and disability progression in people with RRMS. These treatments are associated with possible medium and long-term side effects, and the risk-benefit balance might be unfavourable;

- IFNß-1a (Avonex), intravenous immunoglobulins, cyclophosphamide, and long-term corticosteroids have an unfavourable risk-benefit balance for people with RRMS;

- there are insufficient high quality data to clarify whether there is a favourable risk-benefit balance using azathioprine;

- nine drugs (IFNß-1b (Betaseron), IFNß-1a (Avonex and Rebif), glatiramer acetate, mitoxantrone, methotrexate, cyclophosphamide, intravenous immunoglobulins, and long-term corticosteroids) were also studied in people with PrMS. Few studies were of high quality and no drug was shown to be effective in preventing disability progression in people with PrMS.

Referrence

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- Yousheng Xiao[1], Mycophenolate mofetil for relapsing-remitting multiple sclerosis,2014

THANK YOU FOR YOUR ATTENTION