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EXECUTIVE SUMMARY

AZATHIOPRINE IN RHEUMATOLOGY

- Azathioprine hypersensitivity syndrome is strikingly common in ANCA-associated vasculitis, might be associated with reduced TPMT activity, is accompanied by an increase in neutrophil counts and may occur even during concomitant prednisolone therapy. Proper recognition may prevent unnecessary hospital procedures and damage to the patient.
- Post hoc analysis of combined trial data suggest that stopping AZA maintenance therapy does not lead to a significant increase in relapse rate and AZA maintenance for more than 18 months after diagnosis does not significantly influence relapse-free survival. ANCA specificity has more effect on relapse-free survival than duration of maintenance therapy and should be used to tailor therapy individually.
- AZA and MTX showed similar efficacy and adverse events in patients with ASyS. Pneumonitis is a rare but important event in patients receiving MTX.
- The long-term follow-up data of the MAINTAIN Nephritis Trial do not indicate that MMF is superior to AZA as maintenance therapy in a Caucasian population suffering from proliferative lupus nephritis. Moreover, we confirm the excellent positive predictive value of an early proteinuria decrease for long-term renal outcome.
- Addition of AZA to glucocorticoids for the induction of remission of nonsevere SNVs does not improve remission rates, lower relapse risk, spare steroids, or diminish the EGPA asthma/rhinosinusitis exacerbation rate.

AZA: Azathioprine,
IBD: Inflammatory Bowel diseases,
MP: Mercaptopurine,
OR: Overall Response,
MTX: Methotrexate,
AD: Atopic Dermatitis,
ANCA: Antineutrophil cytoplasmic antibodies,
TPMT: Thiopurine methyltransferase,
MMF: Mycophenolate Mofetil,
ASyS: antisynthetase syndrome,
SNVs: Systemic necrotizing vasculitides,
EGPA: Eosinophilic Granulomatosis with Polyangiitis,
LN: Lupus Nephritis,
CsA: cyclosporine
CRR: Complete Renal Remission, prednisone (PRED)

AZATHIOPRINE IN RHEUMATOLOGY

CLINICAL TRIALS

Azathioprine Hypersensitivity Syndrome in a Cohort of ANCA-Associated Vasculitis Patients

Arno Hessels, Jan Stephan Sanders.et.al.

Rheumatology, Volume 58, Issue Supplement_2, March 2019, kez059.020. 3

Long term azathioprine maintenance therapy in ANCA-associated vasculitis:

Combined results of long-term follow-up data

Anoek A E de Joode.et.al.

Rheumatology, Volume 56, Issue 11, November 2017. 4

Efficacy and adverse effects of methotrexate compared with azathioprine in the antisynthetase syndrome

M. Casal-Dominguez.et.al.

Clinical and Experimental Rheumatology 2019. 5

Long-term follow-up of the MAINTAIN Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis

Farah Tamirou.et.al.

Ann Rheum Dis. 2016 Mar; 75(3):526-31. 6

RANDOMIZED CONTROLLED TRIALS

Adding Azathioprine to Remission Induction Glucocorticoids for Eosinophilic Granulomatosis with Polyangiitis (Churg Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa without Poor Prognosis Factors: A Randomized, Controlled Trial

Xavier Puéchal MD.et.al.

Arthritis & Rheumatology Vol. 69, No. 11, November 2017. 7

Clinical Trials

Azathioprine Hypersensitivity Syndrome in a Cohort of ANCA-Associated Vasculitis Patients

Arno Hessels, Jan Stephan Sanders.et.al.

Rheumatology, Volume 58, Issue Supplement_2, March 2019, kez059.020,

Background and Aims

Azathioprine hypersensitivity syndrome is a rare complication of azathioprine therapy. Its manifestations (malaise, myalgia, high CRP and skin eruption) resemble infection or relapse of inflammatory disease, hindering correct diagnosis. Current literature is limited to sporadic case reports and reviews. We sought to estimate the incidence of azathioprine hypersensitivity syndrome and describe its characteristics in the context of an observational cohort of ANCA-associated vasculitis patients, in order to facilitate early recognition and awareness among clinicians.

Method

Within a cohort of 290 ANCA-associated vasculitis patients receiving azathioprine maintenance therapy, frequency of azathioprine hypersensitivity was described and characteristics were compared between hypersensitive and non-hypersensitive patients. Clinical picture, laboratory abnormalities and concurrent medication of patients with azathioprine hypersensitivity were described.

Result

Of 290 patients, 25 (9%) experienced azathioprine hypersensitivity a median of 14 (IQR 12-18) days after starting azathioprine. Frequent symptoms were fever (100%), malaise (60%), arthralgia (36%) and rash (32%). All patients used prednisolone (median 10mg/d, IQR 9.4-16.3mg/d) at the time of the hypersensitivity reaction. A significant rise in CRP (100%) leukocyte counts (58%) and neutrophil counts (50%) were documented, but no eosinophilia. Thiopurine S-methyltransferase (TPMT) activity was significantly lower in hypersensitive patients (median 74.4 [IQR 58.0-80.1]nmol/gHb/l) compared to controls (median 81.4 [71.9-90.5] nmol/gHb/l), P = 0.01. Hypersensitive patients had a higher risk of relapse (HR 2.2, 95% CI 1.2-4.2; P = 0.01).

Conclusion

Azathioprine hypersensitivity syndrome is strikingly common in ANCA-associated vasculitis, might be associated with reduced TPMT activity, is accompanied by an increase in neutrophil counts and may occur even during concomitant prednisolone therapy. Proper recognition may prevent unnecessary hospital procedures and damage to the patient.

https://pubmed.ncbi.nlm.nih.gov/30368003/

Clinical Trials

Long term azathioprine maintenance therapy in ANCA-associated vasculitis: combined results of long-term follow-up data

Anoek A E de Joode.et.al.

Rheumatology, Volume 56, Issue 11, November 2017.

Background and Aims

We studied whether in ANCA-associated vasculitis patients, duration of AZA maintenance influenced relapse rate during long-term follow-up.

Method

Three hundred and eighty newly diagnosed ANCA-associated vasculitis patients from six European multicentre studies treated with AZA maintenance were included; 58% were male, median age at diagnosis 59.4 years (interquartile range: 48.3–68.2 years); granulomatosis with polyangiitis, n = 236; microscopic polyangiitis, n = 132; or renal limited vasculitis, n = 12. Patients were grouped according to the duration of AZA maintenance after remission induction: ≤18 months, ≤24 months, ≤36 months, ≤48 months or > 48 months. Primary outcome was relapse-free survival at 60 months.

Result

During follow-up, 84 first relapses occurred during AZA-maintenance therapy (1 relapse per 117 patient months) and 71 after withdrawal of AZA (1 relapse/113 months). During the first 12 months after withdrawal, 20 relapses occurred (1 relapse/119 months) and 29 relapses >12 months after withdrawal (1 relapse/186 months). Relapse-free survival at 60 months was 65.3% for patients receiving AZA maintenance >18 months after diagnosis vs 55% for those who discontinued maintenance ≤18 months (P = 0.11). Relapse-free survival was associated with induction therapy (i.v. vs oral) and ANCA specificity (PR3-ANCA vs MPO-ANCA/negative).

Conclusion

Post hoc analysis of combined trial data suggest that stopping AZA maintenance therapy does not lead to a significant increase in relapse rate and AZA maintenance for more than 18 months after diagnosis does not significantly influence relapse-free survival. ANCA specificity has more effect on relapse-free survival than duration of maintenance therapy and should be used to tailor therapy individually.

https://pubmed.ncbi.nlm.nih.gov/28977502/

AZATHIOPRINE IN RHEUMATOLOGY

Clinical Trials

Efficacy and adverse effects of methotrexate compared with azathioprine in the antisynthetase syndrome

M. Casal-Dominguez.et.al.

Clinical and Experimental Rheumatology 2019.

Background and Aims

We compared the clinical outcomes in ASyS patients treated with AZA versus MTX including change in corticosteroid dose, strength, and creatine kinase (CK) as well as the prevalence of adverse effects.

Method

We compared the clinical outcomes in ASyS patients treated with AZA versus MTX including change in corticosteroid dose, strength, and creatine kinase (CK) as well as the prevalence of adverse effects.

Result

Among 169 patients with ASyS, 102 were treated at some point exclusively with either AZA or MTX (± corticosteroids). There were no significant differences in the rate of muscle strength recovery, CK decrease or corticosteroid tapering between those ASyS patients treated with MTX versus AZA. The prevalence of adverse events in patients treated with AZA and MTX was similar (29% vs. 25%, p>0.05); elevated liver enzymes (17% AZA vs. 12% MTX) and gastrointestinal involvement (10% AZA vs. 8% MTX) were the most common adverse events. While no patients treated with AZA developed lung complications, two of the patients treated with MTX experienced reversible pneumonitis with MTX cessation.

Conclusion

AZA and MTX showed similar efficacy and adverse events in patients with ASyS. Pneumonitis is a rare but important event in patients receiving MTX.

https://pubmed.ncbi.nlm.nih.gov/31074729/

Clinical Trials

Long-term follow-up of the MAINTAIN Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis

Farah Tamirou.et.al.

Ann Rheum Dis. 2016 Mar; 75(3):526-31.

Background and Aims

To report the 10-year follow-up of the MAINTAIN Nephritis Trial comparing azathioprine (AZA) and mycophenolate mofetil (MMF) as maintenance therapy of proliferative lupus nephritis, and to test different definitions of early response as predictors of long-term renal outcome.

Method

In 2014, data on survival, kidney function, 24 h proteinuria, renal flares and other outcomes were collected for the 105 patients randomised between 2002 and 2006, except in 13 lost to follow-up.

Result

Death (2 and 3 in the AZA and MMF groups, respectively) and end-stage renal disease (1 and 3, respectively) were rare events. Time to renal flare (22 and 19 flares in AZA and MMF groups, respectively) did not differ between AZA and MMF patients. Patients with good long-term renal outcome had a much more stringent early decrease of 24 h proteinuria compared with patients with poor outcome. The positive predictive value of a 24 h proteinuria <0.5 g/day at 3 months, 6 months and 12 months for a good long-term renal outcome was excellent (between 89% and 92%). Inclusion of renal function and urinalysis in the early response criteria did not impact the value of early proteinuria decrease as long-term prognostic marker.

Conclusion

The long-term follow-up data of the MAINTAIN Nephritis Trial do not indicate that MMF is superior to AZA as maintenance therapy in a Caucasian population suffering from proliferative lupus nephritis. Moreover, we confirm the excellent positive predictive value of an early proteinuria decrease for long-term renal outcome.

https://pubmed.ncbi.nlm.nih.gov/25757867/

AZATHIOPRINE IN RHEUMATOLOGY

RCT'S

Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa without Poor Prognosis Factors: A Randomized, Controlled Trial

Xavier Puéchal MD.et.al.

Arthritis & Rheumatology Vol. 69, No. 11, November 2017.

Background and Aims

In most patients with nonsevere systemic necrotizing vasculitides (SNVs), remission is achieved with glucocorticoids alone, but one-third experience a relapse within 2 years. This study was undertaken to determine whether the addition of azathioprine (AZA) to glucocorticoids could achieve a higher sustained remission rate of newly diagnosed nonsevere eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA), microscopic polyangiitis (MPA), or polyarteritis nodosa (PAN).

Method

All patients included in this double-blind trial received glucocorticoids, gradually tapered over 12 months, and were randomized to receive AZA or placebo for 12 months, with stratification according to SNV (EGPA or MPA/PAN). The primary end point was the combined rate of remission induction failures and minor or major relapses at month 24.

Result

Ninety-five patients (51 with EGPA, 25 with MPA, and 19 with PAN) met the inclusion criteria, were randomized, and received at least 1 dose of AZA (n = 46) or placebo (n = 49). At month 24, 47.8% of the patients receiving AZA versus 49% of the patients receiving placebo had remission induction failures or relapses (P = 0.86). Secondary end points were comparable between the AZA and placebo arms. These included initial remission rate (95.7% versus 87.8%), total relapse rate (44.2% versus 40.5%), and glucocorticoid use. Two patients in the placebo arm died; 22 patients in the AZA arm (47.8%) and 23 patients in the placebo arm (46.9%) experienced =1 severe adverse event. For EGPA patients, the primary end point (48% in the AZA arm versus 46.2% in the placebo arm) and the percent of patients who experienced asthma/rhinosinusitis exacerbations (24% in the AZA arm versus 19.2% in the placebo arm) were comparable between treatment arms.

Conclusion

Addition of AZA to glucocorticoids for the induction of remission of nonsevere SNVs does not improve remission rates, lower relapse risk, spare steroids, or diminish the EGPA asthma/rhinosinusitis exacerbation rate.

https://pubmed.ncbi.nlm.nih.gov/28678392/