Cyclosporine in the era of biologics: a mini-review with special emphasis on the possible use in combination with biologics for psoriasis

Nicoletta Cassano
Gino A. Vena

Unit of Dermatology and Venereology, Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy

Address for correspondence:
Gino A. Vena, MD
Dermatology Clinic, DIMO Department
University of Bari - Policlinico
Piazza Giulio Cesare, 11
70124 Bari, Italy
Phone and Fax: +39 080 5478920
E-mail: ginoantonio.vena@uniba.it

Summary

Combination of systemic biological and traditional agents is increasingly used for the treatment of "high-need" patients with psoriasis. There are only limited data on the combination of cyclosporine with biological drugs for the treatment of psoriatic disease. This article briefly reviews the available information on this combination strategy.

KEY WORDS: psoriasis; cyclosporine; anti-TNF treatment; biological drugs; combination therapy.

Introduction

Combination therapy is an important strategy for the management of plaque psoriasis and is aimed at optimizing the effectiveness and tolerability of treatment. Combination of systemic biologic and non-biologic agents is increasingly considered for the treatment of "high-need" patients with moderate-to-severe psoriasis, especially in those with particularly severe and refractory disease (1, 2). In fact, data from recent European reports have indicated that biological therapy is given concomitantly with traditional systemic drugs in up to 30% of psoriasis patients (3-5).
The association of anti-tumor necrosis factor (TNF) drugs with disease-modifying antirheumatic drugs (DMARDs) is often taken into consideration in rheumatological practice, and, in particular, combination treatment with methotrexate (MTX) has been extensively studied and used in rheumatologic indications, especially rheumatoid arthritis (RA). More in detail, the use of MTX is strongly recommended for the treatment of RA with TNF blockers, particularly anti-TNF monoclonal antibodies, as this DMARD has proved to be capable of reducing the formation of anti-drug neutralizing antibodies and the clearance of biological drugs.
However, the use of immunosuppressive drugs in combination with biologics in psoriasis is generally not indicated; therefore, the risk/benefit ratio of this "off-label" approach should be cautiously considered. In psoriasis, in spite of the ever-growing importance of combination therapies in clinical practice, the literature contains very few data on the combination of biologics and conventional systemic drugs. Compared to MTX, even more limited information exists about the role of cyclosporine (CsA) as a part of the combination strategy.
This article briefly presents an overview on the use of oral CsA in combination with biologics in psoriatic disease, focusing the attention on anti-TNF drugs, as there are no data on ustekinumab, and adding a short mention to efalizumab, whose market authorization was discontinued in 2009. This review does not include biologic drugs which are available only in other countries (i.e., alefacept).

Methods

The PubMed (MEDLINE) and EMBASE databases were searched using the terms 'psoriasis', 'combination', 'cyclosporin(e)', 'etanercept', 'infliximab', 'adalimumab', and 'efalizumab'. Searches were limited to clinical studies involving adults that were published in English. References were checked for additional sources. The most important information on experimental studies and rheumatological experience in RA and psoriatic arthritis (PsA) with anti-TNF agents and CsA was also added using the above-mentioned data sources.

Data synthesis

General data and use in RA patients

Possible synergistic effects of CsA and anti-TNF-alpha drugs were shown in experimental models (6). In particular, the activity of either the single drug or their combination was investigated in type II collagen-immunized DBA/1 mice with arthritis, comparing such treatments with a control consisting in saline. CsA improved arthritis and suppressed interferon (IFN)-gamma production by CD4+ T cells. CsA also reduced the expression of TNF-alpha in affected joints through the reduction in Th1 cell-mediated response while TNF-alpha production by macrophages was not directly affected by the drug. Anti-TNF-alpha therapy was found to diminish IFN-gamma production by T lymphocytes.

In an open-label study, multiple intravenous infusions of 3 mg/kg infliximab were given for 12 months in 18 patients with refractory RA receiving CsA (2 mg/kg/day) and prednisone (5 mg/day) (7). The combination treatment with CsA, prednisone and infliximab led to the achievement of the American College of Rheumatology (ACR) 20 response criteria in 80% of patients while the ACR 50 response rate was 39%. Overall tolerability was good in most patients; treatment withdrawal was required in two cases because of adverse reactions, represented by an acute hypersensitivity reaction and pulmonary tuberculosis, respectively. Based on this experience, authors' opinion supported the possible role of CsA as alternative DMARD to be used in combination with infliximab in patients with refractory RA who are unresponsive or intolerant to MTX (7).
Open-label studies in small series of RA patients evaluated the addition of CsA to infliximab and MTX showing controversial results and overall minor evidence for convincing beneficial effects (8-10).
Isolated case reports documented the safety of combination therapy with CsA and TNF-alpha blockers (adalimumab and etanercept) in RA patients and concomitant HCV infection (11).

Use in psoriatic disease

There are an overall paucity of reports and a lack of general consensus regarding the use of conventional systemic drugs and biologics in psoriasis, despite the frequent use of such combination regimens in clinical practice. Very limited data are available on the use of CsA combined with biologics for psoriasis.
Some reports evaluated transition from CsA to biologics, such as etanercept or efalizumab, in patients requiring CsA discontinuation (12-14). In such circumstances, especially in severe refractory cases, transient overlapping of biologic therapy and CsA can be considered, and CsA dose can be gradually tapered in order to prevent flare-up or rebound of cutaneous lesions.
CsA might be part of sequential treatment approach to psoriasis. For instance, CsA can be used in patients who need to discontinue biological therapy in order to avoid rebound or to maintain clinical response (14). In patients receiving intermittent treatment with etanercept, sequential use of cyclosporine might be useful in selected cases to postpone psoriasis relapse. Maintenance CsA low-dose schemes may be helpful for this purpose, including the "week-end" regimen (15).
Of note, the results of a small open-label pilot study indicated that treatment with only 2 infliximab infusions caused a striking improvement of psoriasis, which could be sustained in most cases by the sequential use of CsA 3 mg/kg/day over a 24-week period in patients who had previously failed to respond to CsA ≥3 mg/kg/day (16). These preliminary results appeared to suggest the possible hypothesis that infliximab can restore the clinical response to conventional treatments previously found as ineffective.
Combined treatment with etanercept and CsA has been successfully used to control generalized pustular psoriasis (17).
CsA has been administered as a rescue option, with or without interruption of biologic therapy, in patients experiencing transitory return of psoriasis lesions during biologic treatment or to manage severe exacerbations of psoriasis, including erythrodermic or generalized pustular psoriasis or *de novo* appearance of psoriasis (14, 18-22).
In a series of 7 patients with psoriasis poorly controlled by conventional treatments, induction therapy with etanercept 50 mg once weekly (QW) and CsA at the daily dosage of 200 mg caused a marked response of skin lesions after a range of 4 to 12 weeks (23). An improvement of the Psoriasis Area and Severity Index (PASI) of at least 50% (PASI 50) was observed in all subjects and 6 of them had also a PASI improvement of 75% or more (PASI 75). Response was then sustained during a subsequent maintenance treatment with CsA 100 mg/day and etanercept 25 mg twice weekly (BIW) for 16-64 weeks (23).
A retrospective analysis reviewed the results obtained with etanercept 50 mg QW and CsA, given at doses in the range 3-5 mg/kg BIW, with an interval of 3-4 days (24). This retrospective study involved 17 patients who required the combination therapy for different reasons: primary inefficacy (n= 4) or secondary inefficacy (reduction of drug efficacy in patients who were previously responders) of etanercept monotherapy (n= 3); persistence of disabling cutaneous lesions at critical sites, despite a significant improvement in the general PASI score (n= 5); flare of psoriasis during etanercept treatment after interruption of efalizumab therapy (n= 5). Patients with concomitant PsA in the case series had PsA symptoms well controlled by etanercept monotherapy. The addition of CsA was capable of inducing a relevant clinical benefit on skin lesions in a total of 12 patients. The combination treatment was well tolerated. Only a patient experienced relevant side effects (repeated hypertensive crises) which caused CsA discontinuation after 2 months.
Very interesting data exist about the use of CsA in association with TNF-alpha inhibitors in PsA (25-27).
A pilot study evaluated 11 PsA patients treated with etanercept 50 mg QW for at least 24 weeks who obtained remission of their PsA with unsatisfactory response of skin lesions (defined by a PASI score of at least 10 despite biological therapy) (25). In such patients the addition of CsA, at a daily dose of 3 mg/kg, to etanercept 50 mg QW was well tolerated and led to the achievement of the PASI 75 in 9 patients after 24 weeks.
In another pilot study, 41 PsA patients were randomized to receive etanercept 50 mg QW in association with CsA (3 mg/kg/day) or etanercept 50 mg QW in combination with MTX (7.5-15 mg/week) for 6 months (26). The two combination regimens were equally effective on PsA symptoms and did not show relevant differences in the rate of adverse events, except for hypertension which was more frequent among CsA-treated patients. Of note, etanercept plus CsA proved to be more efficacious than etanercept plus MTX in controlling skin lesions, with the former regimen being associated with PASI 50 and PASI 75 responses at 6 months in 88% and 53% of cases versus 73% and 32% of patients treated with etanercept and MTX.
There are only anecdotal reports on combination therapy with adalimumab and CsA for psoriasis, that documented mixed efficacy results (28).

Interesting considerations can be drawn by the results of a prospective 12-month open-label trial, evaluating the combination of adalimumab and CsA in patients with severely active PsA and inadequate response to MTX (27). The combined therapy proved to be safe and seemed to produce an overall major clinical improvement. In this trial, 57, 58, and 55 patients were treated with CsA (2.5-3.75 mg/kg/day), adalimumab (40 mg every other week), or combination of both drugs, respectively. At 12 months, the Psoriatic Arthritis Response Criteria were obtained by 65% of patients who received CsA alone (p=0.0003 in favor of combination treatment), 85% of adalimumab-treated patients (p=0.15 vs combination treatment), and 95% of patients treated with the combination, while the ACR 50 response rates were 36%, 69%, and 87%, respectively (p<0.0001 and p=0.03 in favor of combination treatment). A significantly greater mean improvement in Health Assessment Questionnaire Disability Index was achieved by combination treatment as compared to CsA or adalimumab alone. In 119 patients who had at least 2.5% of body surface area affected by psoriatic plaques at baseline, all three treatment modalities caused a significant improvement of psoriasis throughout the entire study period. At 6 months, the PASI 50 and PASI 75 response rates were 55% and 25% for the CsA group, 44% and 23% for the adalimumab group and 71% and 37% for the combination group. At the end of the study, 84.1% and 68.2% of patients who received combination treatment reached the PASI 50 and PASI 75, respectively. Notably, at 12 months, combination therapy significantly improved psoriasis beyond adalimumab, but not beyond the effect of CsA monotherapy.

Conclusions

Limited data are available on the use of CsA in combination with biologics for psoriatic disease. The few available data seem to suggest the safe and effective use of CsA in combination with anti-TNF biologics in psoriatic disease. This combination strategy might be used in selected cases for short periods of time, i.e. as a rescue therapy aimed at potentiating or restoring clinical response to anti-TNF drugs, before considering switch to an alternative biologic drug (29).

Despite these encouraging data, it has to be highlighted that the use of immunosuppressive drugs is not indicated in combination with biologics in psoriasis, and therefore a careful assessment of the risk/benefit ratio should be recommended and be individually considered. The possible synergistic effects of the combination also imply the enhancement of immunosuppression, with potential risk of deleterious effects particularly with high dosages and prolonged treatment periods. Most of the published reports concerned the association of CsA with etanercept, possibly because of the peculiar mode of action and the less immunosuppressive activity of etanercept compared to anti-TNF antibodies (30).

The combination of CsA and biologics warrants further investigation in psoriatic disease, as well in other inflammatory immune-mediated conditions.

References

1. Lebwohl M. Combining the new biologic agents with our current psoriasis armamentarium. J Am Acad Dermatol 2003;49(2 Suppl):S118-24.
2. Cather JC, Menter A. Combining traditional agents and biologics for the treatment of psoriasis. Semin Cutan Med Surg 2005;24:37-45.
3. Warren RB, Brown BC, Lavery D, Ashcroft DM, Griffiths CE. Biologic therapies for psoriasis: practical experience in a U.K. tertiary referral centre. Br J Dermatol 2009;160:162-9.
4. Driessen RJB, Boezeman JB, van de Kerkhof PCM, de Jong EM. Three-year registry data on biological treatment for psoriasis: the influence of patient characteristics on treatment outcome. Br J Dermatol 2009;160:670-5.
5. Esposito M, Gisondi P, Cassano N, Ferrucci G, Del Giglio M, Loconsole F, Giunta A, Vena GA, Chimenti S, Girolomoni G. Survival rate of anti-TNF alpha treatments for psoriasis in routine dermatological practice: a multicenter observational study. Submitted
6. Williams RO, Mauri C, Mason LJ, Marinova-Mutafchieva L, Ross SE, Feldmann M, Maini RN. Therapeutic actions of cyclosporine and anti-tumor necrosis factor alpha in collagen-induced arthritis and the effect of combination therapy. Arthritis Rheum 1998;41:1806-12.
7. Temekonidis TI, Georgiadis AN, Alamanos Y, Bougias DV, Voulgari PV, Drosos AA. Infliximab treatment in combination with cyclosporin A in patients with severe refractory rheumatoid arthritis. Ann Rheum Dis 2002;61:822-5.
8. Ferraccioli GF, Assaloni R, Di Poi E, Gremese E, De Marchi G, Fabris M. Rescue of combination therapy failures using infliximab, while maintaining the combination or monotherapy with methotrexate: results of an open trial. Rheumatology (Oxford) 2002;41:1109-12.
9. Marchesoni A, Sarzi Puttini P, Gorla R, Caporali R, Arnoldi C, Atzeni F, Vianelli M, Pallavicini FB. Cyclosporine in addition to infliximab and methotrexate in refractory rheumatoid arthritis. Clin Exp Rheumatol 2005;23:916-7.
10. Sidiropoulos PI, Siakka P, Raptopoulou A, Mamoulaki M, Choulaki C, Koutala H, Kouroumali H, Kritikos H, Boumpas DT. An open label, single dose study to evaluate the safety, efficacy, and effects on CD25 expression of ciclosporin in patients with active rheumatoid arthritis despite treatment with methotrexate and infliximab. Ann Rheum Dis 2006; 65:538-41
11. Giannitti C, Benucci M, Caporali R, Manganelli S, Bellisai F, Sebastiani GD, Galeazzi M. Efficacy and safety of anti-TNF-alpha therapy combined with cyclosporine A in patients with rheumatoid arthritis and concomitant hepatitis C virus infection. Int J Immunopathol Pharmacol 2009;22:543-6.
12. Ortiz A, Yamauchi PS.A treatment strategy for psoriasis: transitioning from systemic therapy to biologic agents. Skinmed 2006;5:285-8.
13. Yamauchi PS, Lowe NJ. Cessation of cyclosporine

therapy by treatment with etanercept in patients with severe psoriasis. J Am Acad Dermatol 2006;54(3 Suppl 2):S135-8.
14. Cassano N, Mastrandrea V, Buquicchio R, Miracapillo A, Loconsole F, Filotico R, Vena GA. Efalizumab in moderate-to-severe plaque psoriasis: a retrospective case series analysis from clinical practice. J Biol Regul Homeost Agents 2008;22:185-93.
15. Colombo D, Cassano N, Altomare G, Giannetti A, Vena GA. Psoriasis relapse evaluation with weekend cyclosporine A treatment: results of a randomized, double-blind, multicenter study. Int J Immunopathol Pharmacol 2010; 23:1143-52.
16. Vena GA, Cassano N, Loconsole F, Malara G, Sciarrone C, Puglisi Guerra A. Sequential treatment of psoriasis with infliximab followed by cyclosporin: Preliminary results of an open-label prospective study. G Ital Dermatol Venereol 2006;141:221-5.
17. Ricotti C, Kerdel FA. Subacute annular generalized pustular psoriasis treated with etanercept and cyclosporine combination. J Drugs Dermatol 2007; 6:738-40.
18. Richetta A, Mattozzi C, Carlomagno V, Maiani E, Carboni V, Giancristoforo S, D'Epiro S, Bruni F, Calvieri S. A case of infliximab-induced psoriasis. Dermatol Online J 2008;14:9.
19. Bruzzese V, Pepe J. Efficacy of cyclosporine in the treatment of a case of infliximab-induced erythrodermic psoriasis. Int J Immunopathol Pharmacol 2009; 22:235-8.
20. Kucharekova M, Winnepenninckx V, Frank J, Poblete-Gutiérrez P. Generalized pustulosis induced by adalimumab in a patient with rheumatoid arthritis - a therapeutic challenge. Int J Dermatol 2008;47 (Suppl 1):25-8.
21. Ephrem G, Jour G, Smith BL. Successful treatment of von Zumbusch generalized pustular psoriasis with cyclosporine after eruption post etanercept injection. J Med Liban 2011;59:168-9.
22. Vine K, Votava HJ, Smith BL. Generalized pustular psoriasis of Zumbusch: case report of successful disease control with cyclosporine and etanercept. Cutis 2012;90:132-6.
23. Lee EJ, Shin MK, Kim NI. A clinical trial of combination therapy with etanercept and low dose cyclosporine for the treatment of refractory psoriasis. Ann Dermatol 2010; 22:138-42.
24. Vena GA, Mastrandrea V, Battaglini S, Loconsole F, Buquicchio R, Cassano N. Combination of etanercept and twice-weekly administration of cyclosporin in psoriasis unsatisfactorily controlled by etanercept monotherapy: A retrospective analysis. Eur J Inflamm 2012;10:239-42.
25. D'Angelo S, Cutro MS, Lubrano E, Leccese P, Mennillo GA, Ferrara N, Olivieri I. Combination therapy with ciclosporin and etanercept in patients with psoriatic arthritis. Ann Rheum Dis 2010;69:934-5.
26. Atzeni F, Boccassini L, Antivalle M, Salaffi F, Sarzi-Puttini P. Etanercept plus ciclosporin versus etanercept plus methotrexate for maintaining clinical control over psoriatic arthritis: a randomized pilot study. Ann Rheum Dis 2011;70:712-4.
27. Karanikolas GN, Koukli EM, Katsalira A, Arida A, Petrou D, Komninou E, Fragiadaki K, Zacharioudaki A, Lasithiotakis I, Giavri E, Vaiopoulos G, Sfikakis PP. Adalimumab or cyclosporine as monotherapy and in combination in severe psoriatic arthritis: results from a prospective 12-month nonrandomized unblinded clinical trial. J Rheumatol 2011;38:2466-74.
28. Philipp S, Wilsmann-Theis D, Weyergraf A, Rotterdam S, Frambach Y, Gerdes S, Mössner R. Combination of adalimumab with traditional systemic antipsoriatic drugs - a report of 39 cases. J Dtsch Dermatol Ges 2012;10:821-837.
29. Atzeni F, Sarzi-Puttini P, Vena GA. Resistant cases of psoriatic arthritis: how to manage them. J Rheumatol Suppl 2009;83:73-5.
30. Altomare G, Ayala F, Berardesca E, Chimenti S, Giannetti A, Girolomoni G, Lotti T, Martini P, Peserico A, Guerra AP, Vena GA. Etanercept provides a more physiological approach in the treatment of psoriasis. Dermatol Ther 2008;21 (Suppl 2):S1-14.